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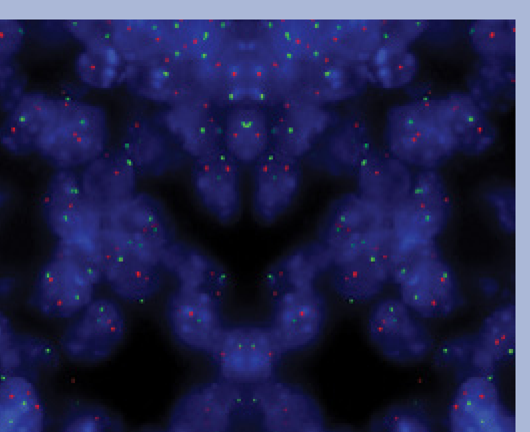
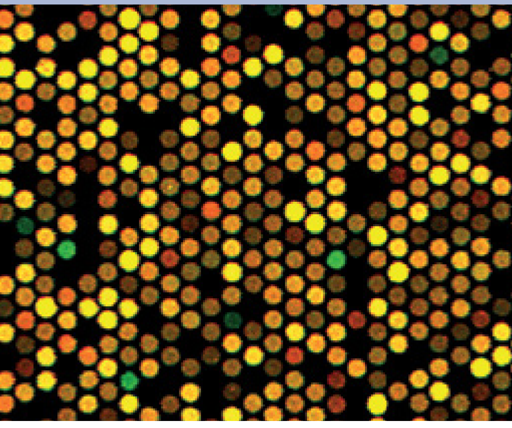




Oxford Gene Technology

Product Catalogue

SECOND EDITION

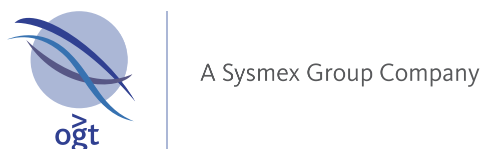
- FISH
- Next Generation Sequencing (NGS)
- Arrays

Oxford Gene Technology (OGT) offers high-quality integrated technologies to detect a complete range of genetic aberrations. Learn more in each of these catalogue sections. To access additional product information and technical resources, visit: www.ogt.com

Cytocell® FISH Probes for Cancer and Inherited Genetic Disease
Comprehensive range of high quality, directly labelled DNA probes for fluorescence *in situ* hybridisation (FISH). Includes a wide range of accessories and custom FISH probes. See page **4**.

SureSeq™ Next Generation Sequencing (NGS) Products for Haematology and Solid Tumour Cancers
An expanding portfolio of NGS panels for cancer research, including myPanel™ custom panel content, library preparation products for the accurate detection of genetic variants, optimised for use with Interpret NGS Analysis Software, a complimentary, powerful and easy-to-use analysis solution. See page **160**.

CytoSure™ Next Generation Sequencing (NGS) and Array Products for Cytogenetics and Rare Disease
A broad range of NGS and array products for constitutional cytogenetics, rare disease and cancer research, including CytoSure Constitutional NGS, a transformative next-generation sequencing panel for intellectual disability (ID) and developmental delay (DD) research. See page **188**.



Oxford Gene Technology - A Sysmex Group Company

Welcome to the new edition of the OGT product catalogue. This expansive volume presents our full portfolio of fluorescence *in situ* hybridisation (FISH) probes, next generation sequencing (NGS) products and arrays.

We're proud to partner with leading researchers by providing tools that contribute to improving the future of clinical care. Whether searching for genetic variants with our SureSeq NGS panels, analysing the variations linked to rare disease and reproductive health using CytoSure arrays and NGS solutions, or selecting from our extensive range of Cytocell FISH probes, our customers know they can rely on OGT for the most advanced and accurate tools available.

As part of the Sysmex group since 2017, we've reinforced our initiatives toward personalised medicine with the development of new products, investing in our technical teams and facilities, and expanding product distribution across the globe. Customers choose OGT not only for the quality of our solutions and the range of products – both catalogue and customised – but also for the product support we offer. We are renowned for our application expertise, and have an experienced network of specialists available to support our complete range of products.

We know that the decision to choose the best genetic analysis products is critical to your success. We thank you for choosing OGT.

John Anson
CEO, Oxford Gene Technology

Please visit our website for technical resources and product news: **www.ogt.com**

Disclaimer

CytoSure™, SureSeq™ and myProbes®: For Research Use Only; Not for Use in Diagnostic Procedures. Cytocell: Product availability may vary from country to country and is subject to varying regulatory requirements. Contact your local representatives for availability.

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* IVD: *In Vitro* Diagnostic Medical Device
† RUO: For Research Use Only. Not for use in diagnostic procedures.

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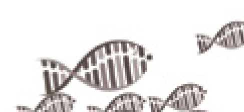

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Cytocell FISH Products

OGT offers an expansive range of Cytocell fluorescence *in situ* hybridisation (FISH) probes aimed at two disciplines: constitutional cytogenetics and haematology/pathology cytogenetics. The Cytocell product range includes:

Aquarius® Range

Aquarius probes are directly labelled liquid probes provided in hybridisation solution. The probes are accompanied by DAPI counterstain to provide a complete fluorescence *in situ* hybridisation kit.

myProbes®

myProbes is a custom FISH probe design and manufacture service, which utilises Cytocell's proprietary BAC clone collection. Previously manufactured myProbes are searchable on www.cytocell.com/custom-search. If a product you require does not appear in the catalogue or online, please contact us (contact@ogt.com). All myProbes products are labelled for Research Use Only (RUO), not for use in diagnostic procedures.

Chromoprobe Multiprobe® Macroarray Range

Using our unique Chromoprobe® process, multiple probes are reversibly bound to a glass slide providing a convenient screening tool for genetic abnormalities across multiple chromosomes. Key applications include use as diagnostic and prognostic tools in the detection of various leukaemias.

Patents and Trademarks

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Cytocell is registered with the UK's MHRA (Medicines and Healthcare products Regulatory Agency) and all Cytocell IVD products are CE marked in accordance with the *In Vitro* Diagnostic Medical Devices Directive 98/79/EC. Product availability may vary from country to country and is subject to varying regulatory requirements. Contact your local representatives for availability.

Quality Management

Cytocell Ltd operates a Quality Management System that has been approved by BSI to ISO 9001:2015, ISO 13485:2016, and the full MDSAP audit criteria. The scope of this approval is applicable to the design, development and manufacture of DNA FISH probes, ancillary products and *in vitro* diagnostic kits and reagents for the detection of chromosomal abnormalities in life science research and diagnostic use.

Cytocell FISH probes are developed and produced in the UK

Additional OGT product information and legal notices

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Tissue Pretreatment Kit (LPS 100): This product is provided under an agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostics or life science use only.

The SureSeq NGS Library Preparation Kit was jointly developed between Oxford Gene Technology and Bioline Reagents Limited.

The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

Disclaimer:

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Every attempt has been made to ensure that the information in this catalogue is correct at time of going to print. Although every care has been taken in preparing this publication, no responsibility or liability will be accepted by Cytocell Ltd, Oxford Gene Technology IP Limited or its employees for its accuracy or completeness.

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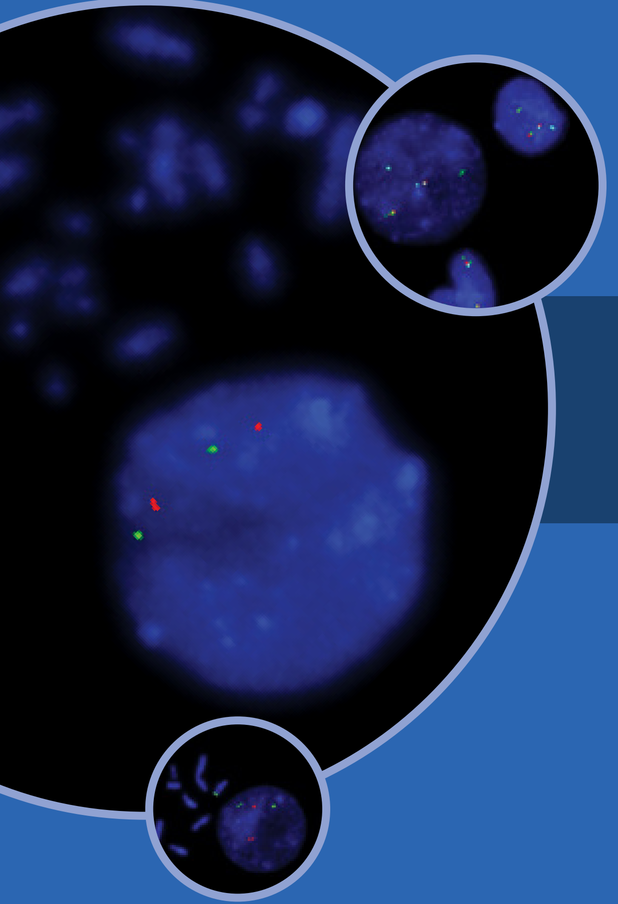

Haematology

Contents

The Cytocell Haematology probe range encompasses a broad range of products to detect genetic aberrations seen in many haematological disorders, such as acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), lymphoma (L), multiple myeloma (MM), myelodysplastic syndrome (MDS), and myeloproliferative neoplasm (MPN).

Cytocell FISH probes are CE-marked IVDs* (unless otherwise indicated).

12 Alpha Satellite 12 *Plus* for CLL
13 AML1 (RUNX1) Breakapart
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53 P53 (TP53) Deletion
54 P53 (TP53)/ATM Probe Combination
55 PDGFRB Breakapart
56 *FAST* PML/RARα (RARA) Translocation, Dual Fusion
57 PML/RARα (RARA) Translocation, Dual Fusion
58 RARα (RARA) Breakapart
59 TCL1 Breakapart
60 TCRAD Breakapart
61 TCRB (TRB) Breakapart
62 TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion
63 TLX1 Breakapart
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Refer to our Haematology key to determine the most commonly associated disease state for each of our Haematology products, as supported by literature.

Haematology key: **

Acute Lymphoblastic Leukaemia

Acute Myeloid Leukaemia

Chronic Lymphocytic Leukaemia

Chronic Myeloid Leukaemia

Lymphoma

Multiple Myeloma

Myelodysplastic Syndrome

Myeloproliferative Neoplasm

* IVD: *In Vitro* Diagnostic Medical Device
† RUO: For Research Use Only. Not for use in diagnostic procedures.
** These roundels are only to provide information supported by the literature and are not a reflection of the intended purpose of this product.

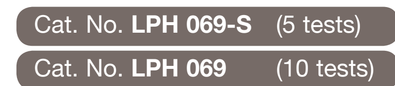
Haematology

As long ago as the 19th century, nuclear changes were recognised as being significant in cancer biology. Advances in cytogenetics and molecular cytogenetics in the last century showed that although a number of numerical and structural chromosome changes appeared to be random and non-specific, rearrangements involving individual chromosomes were shown to define specific abnormalities in individual tumour types.

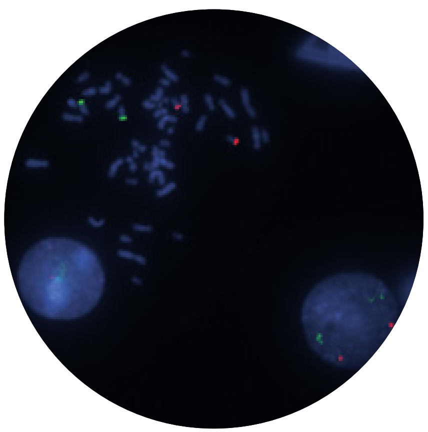
Fluorescence *in situ* hybridisation (FISH), using locus-specific probes that are capable of defining these stereotypic structural rearrangements, has now become a routine diagnostic test in the clinical laboratory and the technique has thus been shown to be useful in the management of cancer patients.

Cytocell offers a range of FISH probes, specific for a number of haematological malignancies, which are available in the Aquarius® liquid format. These probes are directly labelled, ready to use in hybridisation buffer and available in economical five, and larger ten, test kits. The protocol is rapid and simple and has been developed to allow co-denaturation of the FISH probe and target DNA simultaneously.

The probe mixtures are designed for use on interphase nuclei and metaphase chromosomes from cultured peripheral blood cells or cultured bone marrow samples.



Alpha Satellite 12 *Plus* for CLL



Trisomy 12 is a recurrent abnormality in CLL, seen in 20% of cases[1] that often appears as the unique cytogenetic aberration (40-60% of cases with trisomy 12)[2].

Patients with trisomy 12 are classified as low-risk in the absence of any other genetic lesions[3].

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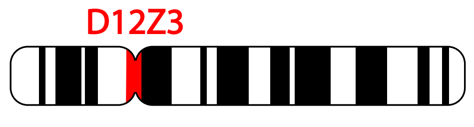

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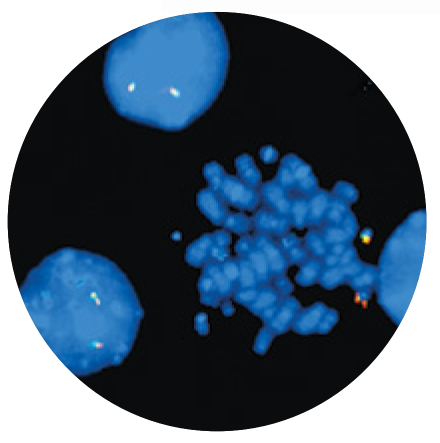
AML1 (RUNX1) Breakapart



The RUNX1 (*RUNX family transcription factor 1*) gene at 21q22.1 is one of the most frequent targets of chromosomal rearrangements observed in human acute leukaemia.

The most common rearrangements are the ETV6-RUNX1 and RUNX1-RUNX1T1 fusions. The ETV6-RUNX1 fusion is brought about by the t(12;21)(p13;q22) translocation, observed in around 21% of childhood B-cell acute lymphoblastic leukaemia (ALL) cases[1], whilst the RUNX1-RUNX1T1 fusion is the result of the t(8;21)(q22;q22) translocation observed in 10-22% of patients with acute myeloid leukaemia (AML) FAB (French-American-British classification) type M2 and 5-10% of AML cases overall[2,3]. Both these rearrangements are considered good prognostic indicators in these diseases[4,5].

The RUNX1 gene is also rearranged in many other rarer translocations, with partners including chromosomes 1, 2, 3, 4, 5, 6, 7, 9, 10, 14, 15, 16, 17, 18, 19, 20 and X[6]. This breakapart probe has been designed to allow the detection of rearrangements regardless of the partner gene.

Rearrangements of RUNX1 are not restricted to translocations. Using FISH, amplifications of chromosome 21 (iAMP21), including the RUNX1 gene, have also been found in childhood ALL[7,8]. These amplifications have been associated with poorer outcome[9].

**

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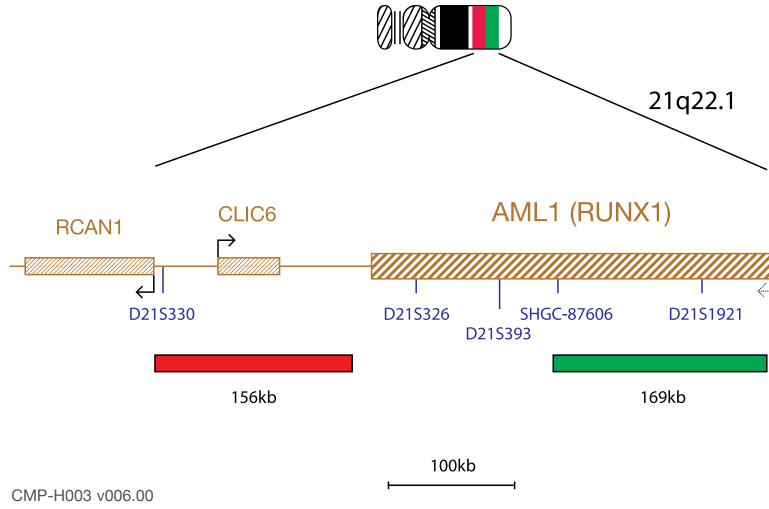

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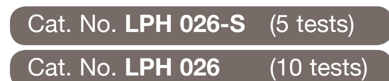
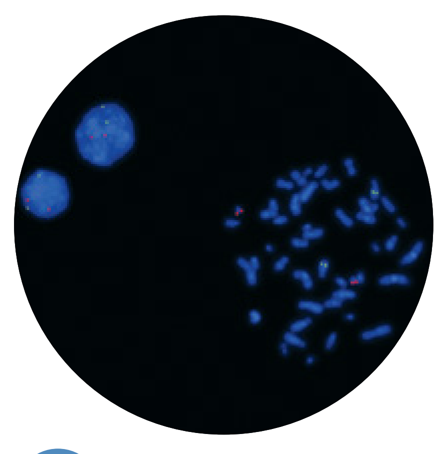


AML1/ETO (RUNX1/ RUNX1T1) Translocation, Dual Fusion



The RUNX1 (*RUNX family transcription factor 1*) gene at 21q22.1 is fused with the RUNX1T1 (*RUNX1 partner transcriptional co-repressor 1*) gene at Ensembl location 8q21.3, in the t(8;21)(q22;q22) translocation, found most commonly in patients with acute myeloid leukaemia (AML) FAB (French-American-British classification) type M2.

AML with a RUNX1-RUNX1T1 fusion resulting from a t(8;21)(q22;q22) translocation is a recognised disease entity according to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia[1]. The translocation is observed in 10-22% of patients with AML FAB type M2 and 5-10% of AML cases overall, most commonly in children and young adults[2] and is a good prognostic indicator[3,4,5]. The t(8;21) breakpoint mainly occurs in the intron between exons 5 and 6, just before the transactivation domain and the fusion protein created contains the DNA-binding domain of RUNX1 fused to the transcription factor RUNX1T1[2].

In addition to the reciprocal t(8;21) translocation creating the RUNX1-RUNX1T1 fusion, variant translocations have also been reported. These variant rearrangements may be cryptic and easily overlooked by G-banding; however, FISH can indicate the presence of such rearrangements[2].

**

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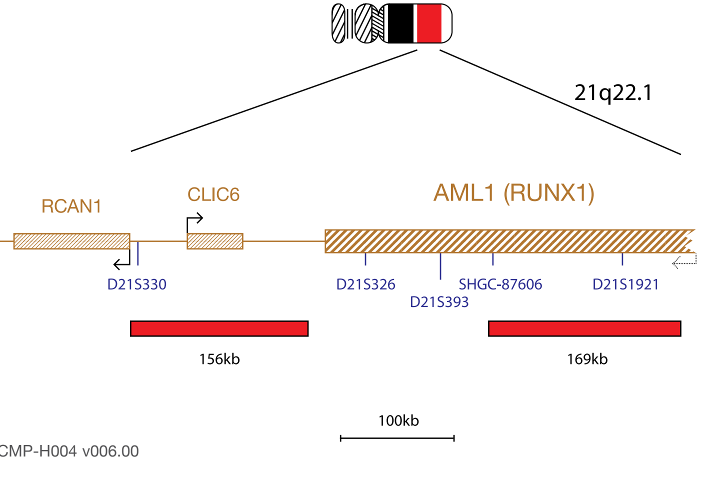

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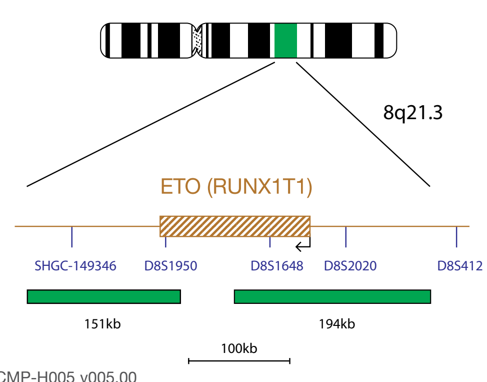

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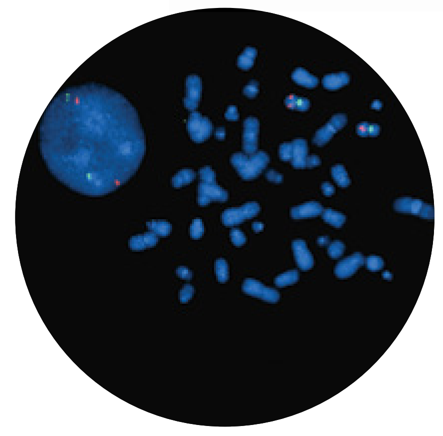
ATM Deletion



The protein kinase ATM (*ATM serine/threonine kinase*) gene at 11q22.3, is frequently deleted in cases of B-cell chronic lymphocytic leukaemia (CLL). ATM is an important checkpoint gene involved in the management of cell damage. Its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway[1].

B-CLL is the most common leukaemia in adults; its course can vary from very indolent to rapidly progressive. Due to the low mitotic activity of the leukaemic cells *in vitro*, clonal chromosomal abnormalities are detected in 40-50%[2] of cases by conventional cytogenetics using B-cell mitogens, whereas FISH analysis identifies chromosomal aberrations in approximately 80%[2] of B-CLLs. Screening for deletions of ATM and/or TP53 is vital to allow informed therapy choices for B-CLL patients, as deletions of TP53 and ATM confer poorer prognosis in this disease[4]; therefore, the use of FISH has proved to be a powerful tool in both the diagnosis and management of patients with B-CLL[2,3,4].

Analysis of the ATM/TP53 interaction in B-CLL has shown that TP53 and ATM play an important role in the proliferation of lymphoid cancer[1]. It has been shown that ATM enhances the phosphorylation of TP53, should the damage be so great that the cell requires destruction by apoptosis (which is mediated by TP53). Deletion of ATM removes this checkpoint activity and hence activation of TP53. Thus, there is no attempt made to repair, or apoptosis of, damaged cells, despite the presence of TP53. In the absence of ATM, damaged cells are allowed to continue to proliferate[5].

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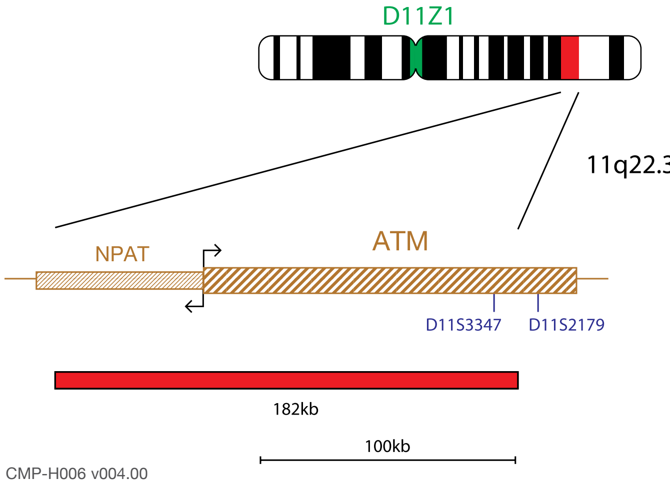

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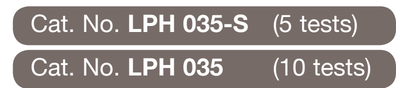
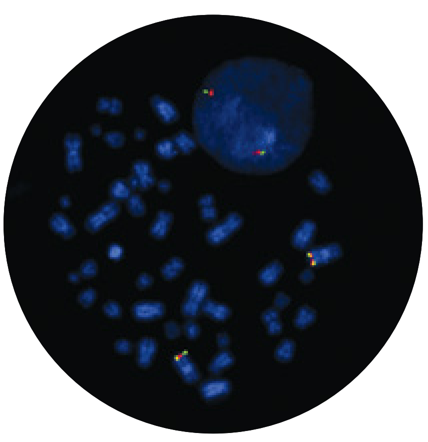


BCL6 Breakapart*



Chromosomal rearrangements involving the BCL6 (*B-cell CLL/ lymphoma 6*) gene at 3q27 are recognised recurrent abnormalities commonly seen in patients with B-cell malignancy[1].

BCL6 rearrangements are the most common chromosomal abnormalities seen in diffuse large B-cell lymphoma (DLBCL), occurring in up to 35% of cases[2]. They are also seen frequently in follicular lymphoma, where they occur in up to 15% of cases[3]. BCL6 is expressed in normal germinal centre B-cells and follicle helper T-cells. BCL6 translocations alter expression by promoter substitution and cause deregulated expression of normal BCL6 protein[1,4].

Approximately 50% of BCL6 translocations will involve one of the three immunoglobulin loci (IGH, IGL or IGK); the remainder of translocations involve one of more than twenty different non-immunoglobulin genes[5]. Additionally, gains and amplifications of the BCL6 gene have also been reported in cases of B-cell lymphoma[6].

The presence of concurrent BCL6 rearrangements with MYC and/or BCL2 rearrangements in patients with 'dual-hit' lymphoma has been shown to be associated with aggressive disease[7].

**

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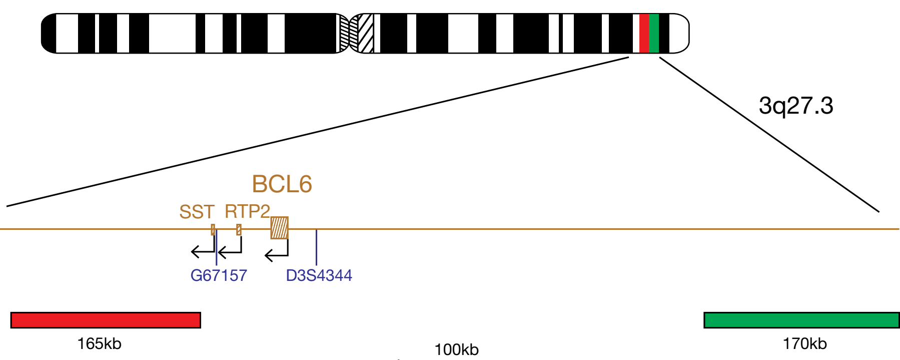

CMP-H007 v004.00

A similar product is also available within the Haematopathology range, refer to page 78.

IVD: *In Vitro* Diagnostic Medical Device

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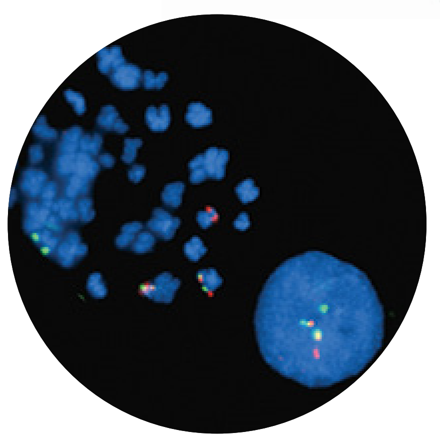
Cat. No. **LPH 007-S** (5 tests)
Cat. No. **LPH 007** (10 tests)

BCR/ABL (ABL1) Dual Fusion Translocation Probe



BCR-ABL (ABL1) positive sample

The BCR (*BCR activator of RhoGEF and GTPase*) gene is located at 22q11.23 and the ABL1 (*ABL proto-oncogene 1, non-receptor tyrosine kinase*) gene is located at 9q34.12. Translocation between these two genes gives rise to the BCR-ABL1 fusion gene, and produces a Philadelphia chromosome; the visible result of this translocation.

The presence of a BCR-ABL1 fusion has important diagnostic and prognostic implications in a number of haematological disorders. The t(9;22)(q34.12;q11.23) translocation is the hallmark of chronic myeloid leukaemia (CML) and is found in around 90-95% of cases[1]. The remaining cases have a variant translocation, or have a cryptic rearrangement involving 9q34 and 22q11.23 that cannot be identified by routine cytogenetic analysis[1].

The BCR-ABL1 fusion can also be found in 25% of adult acute lymphoblastic leukaemia (ALL) and in 2-4% of childhood ALL[1]. The presence of a BCR-ABL1 fusion has been shown to confer a poor prognosis in ALL in both adults and children[1,2]. The detection of the abnormality is therefore of high importance for risk stratification, which will influence treatment and management decisions[2]. In a small number of ALL cases, the translocation does not result in a cytogenetically visible Philadelphia chromosome. In these cases, FISH is essential for highlighting the fusion gene[3].

This rearrangement is also seen in rare cases of acute myeloid leukaemia (AML). Philadelphia-positive AML is characterised by its resistance to conventional standard chemotherapy and poor prognosis[4], so accurate and rapid identification of this chromosomal abnormality is vital.

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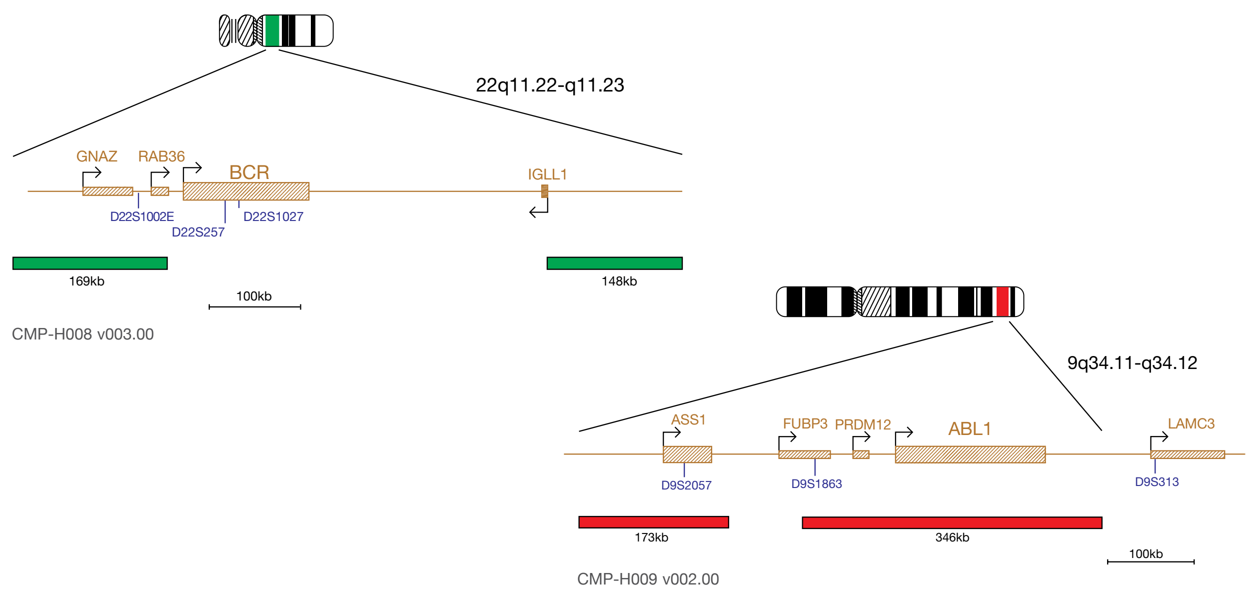

IVD: *In Vitro* Diagnostic Medical Device
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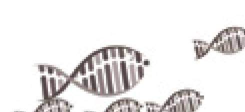
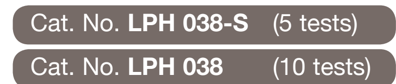
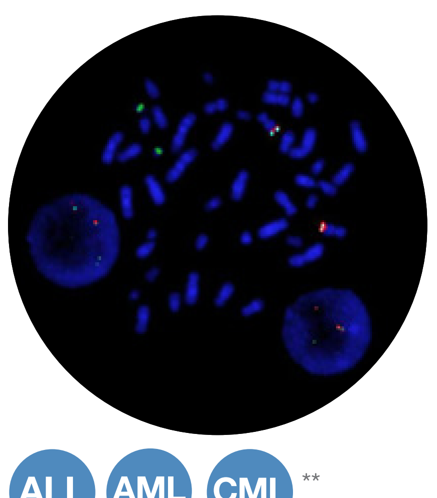




BCR/ABL (ABL1) *Plus* Translocation, Dual Fusion



The BCR (*BCR activator of RhoGEF and GTPase*) gene is located at 22q11.23, the ABL1 (*ABL proto-oncogene 1, non-receptor tyrosine kinase*) gene is located at 9q34.12 and the ASS1 (*argininosuccinate synthase 1*) gene is located at 9q34.11. Translocation between BCR and ABL1 gives rise to the BCR-ABL1 fusion gene, and produces a Philadelphia chromosome; the visible result of this translocation.

The presence of a BCR-ABL1 fusion has important diagnostic and prognostic implications in a number of haematological disorders.

The t(9;22)(q34.12;q11.23) translocation is the hallmark of chronic myeloid leukaemia (CML) and is found in around 90-95%[1] of cases. The remaining cases have a variant translocation, or have a cryptic translocation between 9q34.12 and 22q11.23 that cannot be identified by routine cytogenetic analysis[1]. BCR-ABL1 fusions can also be found in 25% of adult acute lymphoblastic leukaemia (ALL) and in 2-4% of childhood ALL[1]. This rearrangement is also seen in rare cases of acute myeloid leukaemia (AML)[2].

The translocation between chromosomes 9 and 22 can be accompanied by loss of proximal sequences on the derivative chromosome 9, including the ASS1 (*argininosuccinate synthase 1*)[3]. Concomitant ASS1 gene deletions have been associated with poorer prognosis in CML, although this may be partially abrogated by treatment with tyrosine kinase inhibitors (TKIs)[4]; therefore, the establishment of atypical patterns in patients with the BCR-ABL1 translocation may have clinical diagnostic and prognostic implications.

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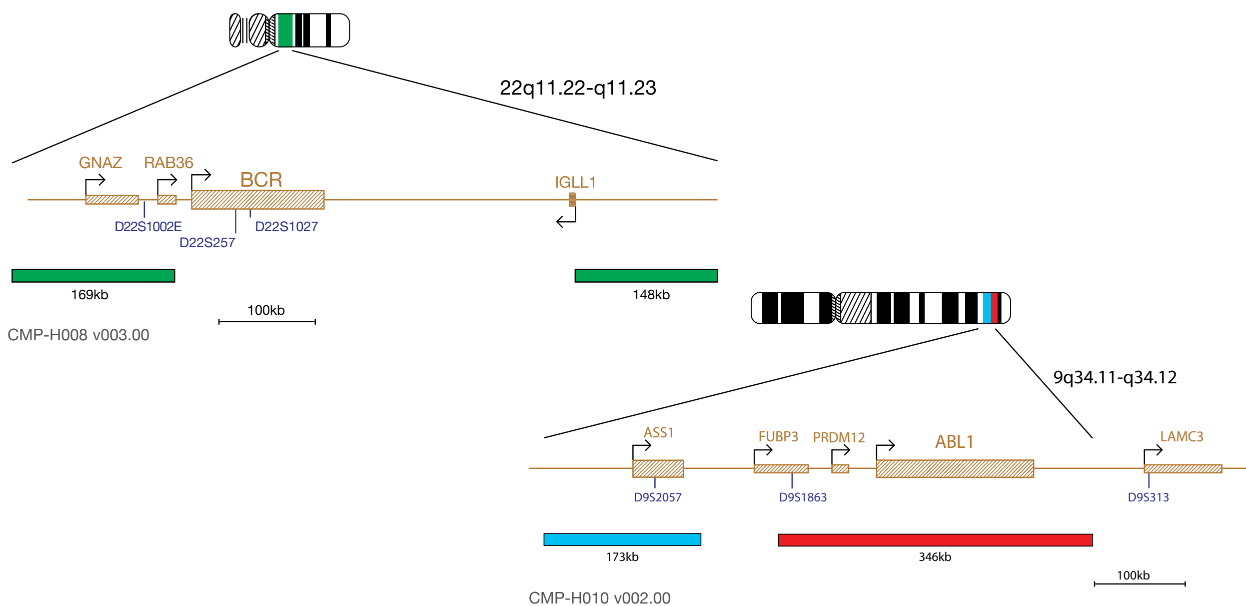

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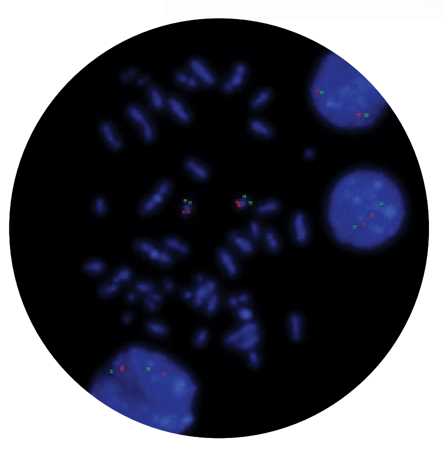
Cat. No. **LPH 022-S** (5 tests)
Cat. No. **LPH 022** (10 tests)

CBFβ (CBFB)/MYH11 Translocation, Dual Fusion



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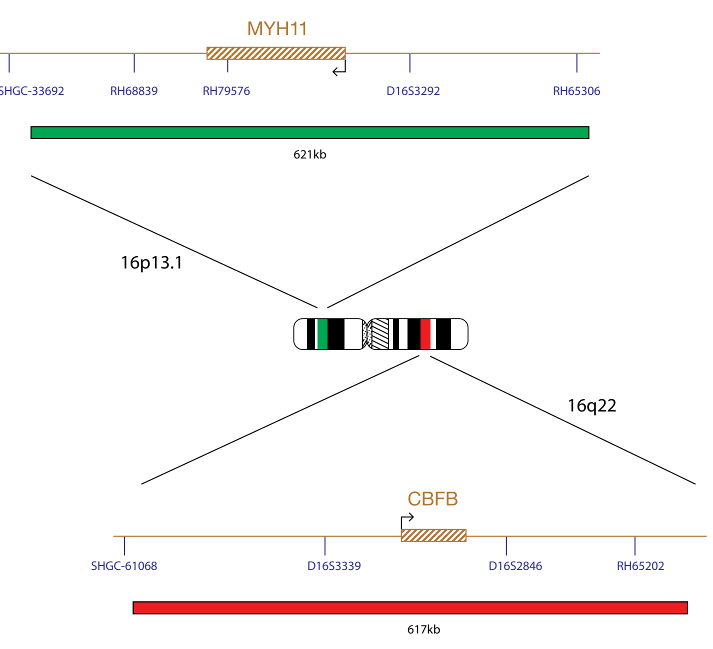
The CBFB (*core-binding factor subunit beta*) gene is located at 16q22 and the MYH11 (*myosin heavy chain 11*) gene is located at 16p13.1. The inversion inv(16)(p13.11q22.1) and the translocation t(16;16)(p13.11;q22.1) give rise to the CBFB-MYH11 fusion gene.

Acute myeloid leukaemias with inv(16)(p13.11q22.1) or t(16;16)(p13.11;q22.1) form a recognised disease entity according to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia[1]. These rearrangements are frequently found in patients with a myelomonocytic subtype with increased bone marrow eosinophils, AML FAB (French-American-British classification) type M4Eo, and are found in 5-8%[1] of all AMLs. Cases of therapy-related AML may also have this rearrangement[1,2].

CBFB-MYH11 rearrangements are classed as a favourable cytogenetic risk group in patients with AML[3,4].

The breakpoints occur in intron 5 of CBFB and intron 5 of MYH11. The N-terminal of CBFB fuses to the C-terminal of MYH11 with its multimerisation domain. The resultant chimaeric protein reduces the amount of active CBF. An accumulation of CBFB-MYH11/CBFA multimers in the nucleus also occurs. CBFB regulates expression of certain ADP-ribosylation factors (ARFs) and other tumour suppressor genes (TSGs) and therefore the fusion protein is thought to repress TSG expression[3].



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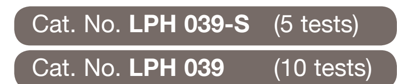
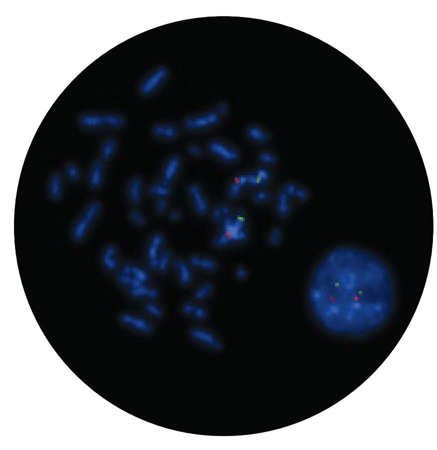


CKS1B/CDKN2C (P18) Amplification/Deletion



The CKS1B (*CDC28 protein kinase regulatory subunit 1B*) gene is located at 1q21.3 and the CDKN2C (*cyclin depended kinase inhibitor 2C*) gene is located at 1p32.3.

Gain of the 1q21 region including CKS1B is one of the most frequently-occurring chromosomal aberrations seen in multiple myeloma[1]. Over-expression of the CKS1B gene up-regulates cell cycle progression, resulting in a more proliferative disease[2]. This is related to the advanced phenotype of multiple myeloma and may therefore be associated with poor prognosis and disease progression[1,2,3]. Gain of 1q21 has been linked to inferior survival and further amplification is observed in disease relapse. Complete gains of the long arm of chromosome 1 are also common in multiple myeloma and can occur as isochromosomes, duplications or jumping translocations and are frequently associated with disease progression[4].

CDKN2C is a tumour suppressor gene responsible for inducing apoptotic cell death and DNA fragmentation[5]. It is up-regulated by the expression of the cytokine IL-6 in multiple myeloma and homozygous deletion of the gene is associated with a more proliferative disease[5]. Although CDKN2C deletions have been reported to be rare in human malignancy, cytogenetic analyses have shown that abnormalities of 1p32-36 occur in around 16% of human multiple myeloma and are associated with worse overall survival[2,3,5,6].

Cytogenetic abnormalities are detected by conventional cytogenetics in about one third of cases of multiple myeloma, but FISH increases the proportion of chromosomal abnormalities to >90%[7].

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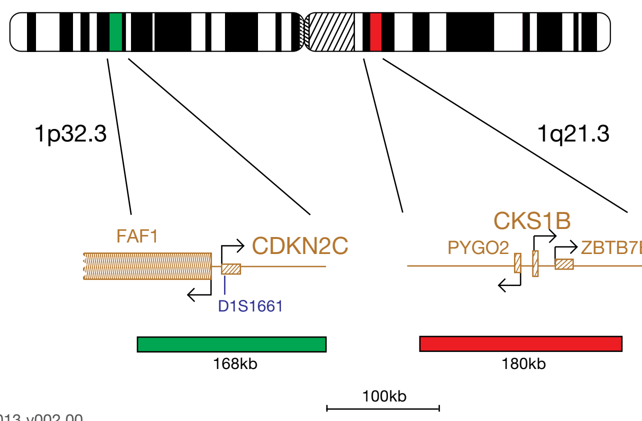

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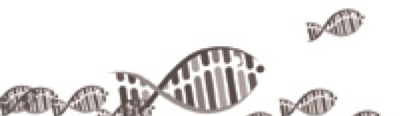

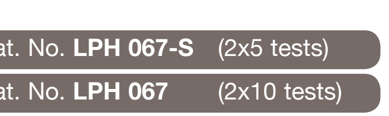

CLL PROFILER Kit

The Cytocell CLL PROFILER Kit is intended to detect deletions of TP53, ATM and D13S319, and gains of the chromosome 12 centromere sequences in peripheral blood or bone marrow samples from patients with chronic lymphocytic leukaemia (CLL).

P53 (TP53)/ATM Probe Combination

The TP53 (*tumor protein p53*) gene at 17p13.1 is one of most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Loss of TP53 is reported in 10% of patients with CLL, and is considered to be the poorest prognostic marker in that disease[1,2]. The ATM (ATM *serine/threonine kinase*) gene at 11q22.3 is an important checkpoint gene involved in the management of cell damage; its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway[3]. Loss of ATM is reported in 18% of patients with CLL, and is considered a poor prognostic marker in that disease[4]. Analysis of the ATM/TP53 interaction in CLL has shown that TP53 and ATM play an important role in the proliferation of lymphoid cancer[3]. It has been shown that ATM enhances the phosphorylation of TP53, should the damage be so great that the cell requires destruction by apoptosis (which is mediated by TP53). Deletion of ATM removes this checkpoint activity and hence activation of TP53. Thus, there is no attempt made to repair, or apoptosis of, damaged cells, despite the presence of TP53. In the absence of ATM, damaged cells are allowed to continue to proliferate[5].

D13S319/13qter/12cen Deletion/Enumeration

Deletions affecting 13q14 are also the most frequent structural genetic aberrations in chronic lymphocytic leukaemia (CLL)[6,7,8]. This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients[9]. The survival rate has been shown to be similar for the two groups[10]. Patients with 13q14 deletions are classified as very low risk, in the absence of any other genetic lesions[1]. Two non-coding RNA genes, DLEU1 (*deleted in lymphocytic leukemia 1*) and DLEU2 (*deleted in lymphocytic leukemia 2*), plus the genetic marker D13S319, span the pathogenic critical region of 13q14[11]. DLEU1 is considered to be the most likely CLL-associated candidate tumour suppressor gene within the 13q14 region[12]. Trisomy 12 is a recurrent abnormality in CLL, seen in 20% of the cases[13] and often appears as the unique cytogenetic aberration (40-60% of cases with trisomy 12)[7]. Patients with trisomy 12 are classified as low-risk in the absence of any other genetic lesions[1].

**

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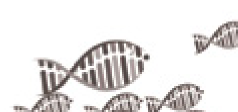

CLL *Plus* Screening Panel

A selection of haematology probes and an alpha-satellite probe for chronic lymphocytic leukaemia (CLL).

Alpha Satellite 12 *Plus* for CLL

Trisomy 12 is a recurrent abnormality in CLL, seen in 20% of cases[1] and often appears as the unique cytogenetic aberration (40-60% of cases with trisomy 12)[2]. Patients with trisomy 12 are classified as low-risk in the absence of any other genetic lesions[3]. This product is also available in 5 (LPH 069-S) and 10 (LPH 069) test kit sizes and has been optimised for overnight hybridisation.

**

13q14.3

Deletions affecting 13q14 are the most frequent structural genetic aberrations in CLL[3,4,5]. This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients[6]. Patients with 13q14 deletions are classified as very low risk, in the absence of any other genetic lesions[3].

P53 (TP53) (17p13)

The TP53 (*tumor protein p53*) gene at 17p13 is one of most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Loss of TP53 is reported in 10% of patients with CLL, and is considered to be the poorest prognostic marker[3,7].

ATM (11q22.3)

The ATM (*ATM serine/threonine kinase*) gene at 11q22.3 is an important checkpoint gene involved in the management of cell damage and its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway[8]. Loss of ATM is reported in 18% of patients with CLL, and is considered a poor prognostic marker in CLL[9].

MYB (6q23.3)

Deletions of chromosome 6q are recurrent in CLL. The MYB (*MYB proto-oncogene, transcription factor*) gene is essential in haematopoietic cell proliferation and differentiation[10,11]. It is located in band 6q23.3 and is provided as a marker for 6q deletion.

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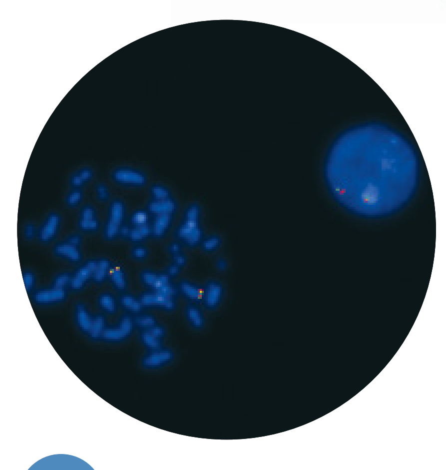
Cytocell aquarius

Cat. No. **LPH 010-S** (5 tests)
Cat. No. **LPH 010** (10 tests)

cMYC (MYC) Breakapart*



Chromosomal rearrangements involving the MYC (*MYC proto-oncogene, bHLH transcription factor*) gene at 8q24 are recognised recurrent abnormalities commonly seen in patients with B-cell malignancy.

MYC rearrangements, activating MYC by translocation with one of the three immunoglobulin loci (IGH, IGL or IGK), are detected in almost all cases of Burkitt lymphoma at diagnosis[1]. They are also seen in diffuse large B-cell lymphoma (DLBCL)[2], multiple myeloma and plasmablastic lymphomas[3,4], amongst other diseases.

MYC has also been shown on rare occasions to be involved in rearrangements with a number of non-immunoglobulin partners[5].

The presence of concurrent MYC rearrangements with BCL2 and/or BCL6 rearrangements in patients with 'dual-hit' lymphoma has been shown to be associated with aggressive disease[6].

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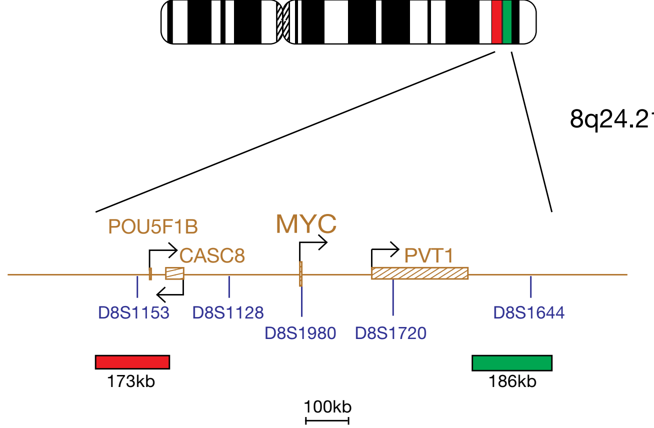

CMP-H014 v003.00

***A similar product is also available within the Haematopathology range, refer to page 87.**

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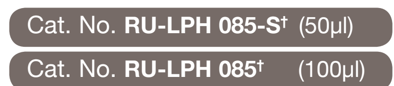
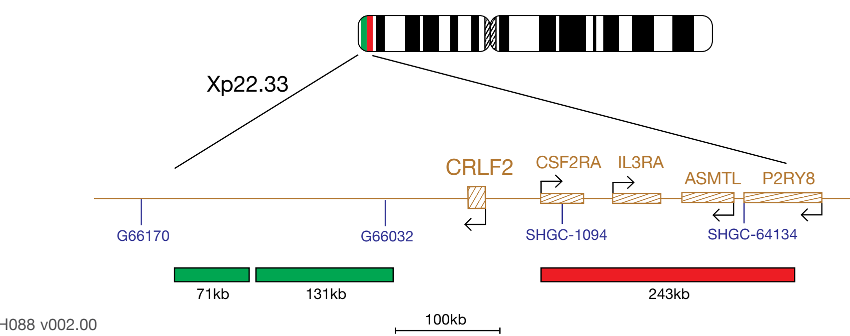


CRLF2 Breakapart†

For research use only

The CRLF2 Breakapart probe consists of a red 243kb probe, which is centromeric to the CRLF2 gene, and two green probes (71kb, 131kb), which are telomeric to CRLF2.

Probe Specification CRLF2, Xp22.33/Yp11.32, Green
CRLF2, Xp22.33/Yp11.32, Red



CMP-H088 v002.00

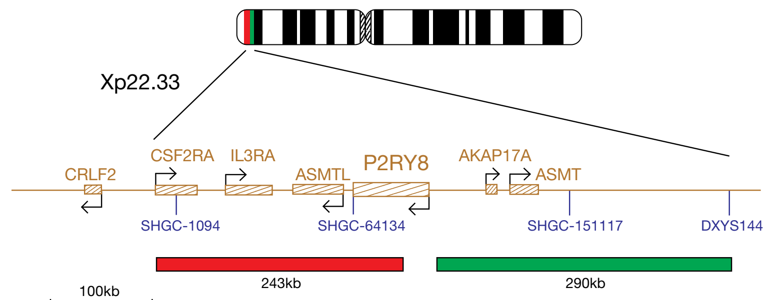
† RUO: For research use only, not for use in diagnostic procedures.

P2RY8 Deletion†

For research use only

The P2RY8 Deletion Probe consists of a red 243kb probe, which covers the telomeric end of P2RY8 and a region distal to the gene, and a green 290kb probe that covers a region to the proximal side of P2RY8.

Probe Specification P2RY8, Xp22.33/Yp11.32, Green
P2RY8, Xp22.33/Yp11.32, Red



CMP-H089 v002.00

† RUO: For research use only, not for use in diagnostic procedures.

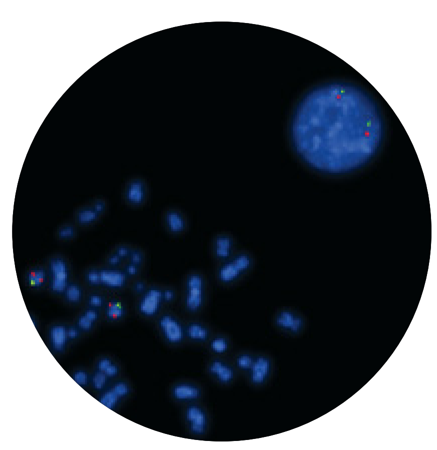
Deletion 13q14.3, D13S319 *Plus* and D13S25

Rearrangements leading to the loss of all or part of the long arm of chromosome 13 are seen frequently in a wide range of haematological disorders.

Chromosome 13q aberrations occur in 16-40% of multiple myeloma cases (MM), most of them being complete monosomy 13 (85%), while the remaining 15% constitute deletion of 13q[1,2,3]. A case study of multiple myeloma patients narrowed down the critical deleted region to 13q14[4]. Historically, deletions of 13q have been associated with poor prognosis in MM but now it is believed that its prognostic relevance may be related to its association with other concurrent genetic lesions[3,5].

Deletions affecting 13q14 are also the most frequent structural genetic aberrations in chronic lymphocytic leukaemia (CLL)[6,7,8]. This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients[9]. The survival rate has been shown to be similar for the two groups[10]. Patients with 13q14 deletions are classified as very low risk, in the absence of any other genetic lesions[11].

Two non-coding RNA genes, DLEU1 (*deleted in lymphocytic leukemia 1*) and DLEU2 (*deleted in lymphocytic leukemia 2*), plus the genetic marker D13S319, span the pathogenic critical region of 13q14[12]. DLEU1 is considered to be the most likely CLL-associated candidate tumour suppressor gene within the 13q14 region[13]. Subsequently, D13S319, located between the RB1 gene and D13S25 and within the DLEU1 locus, was found to be deleted in 44% of CLL cases[14]. It has also been postulated that a gene telomeric to the D13S319 region, encompassing D13S25, may be important in cases with hemizygous deletions and that this gene is a putative tumour suppressor gene[15].



13q14.3 Deletion

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12. Liu Y *et al*., Oncogene 1997;15:2463-73
13. Wolf S *et al*., Hum Mol Genet 2001;10:1275-85
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IVD: *In Vitro* Diagnostic Medical Device
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13q14.3

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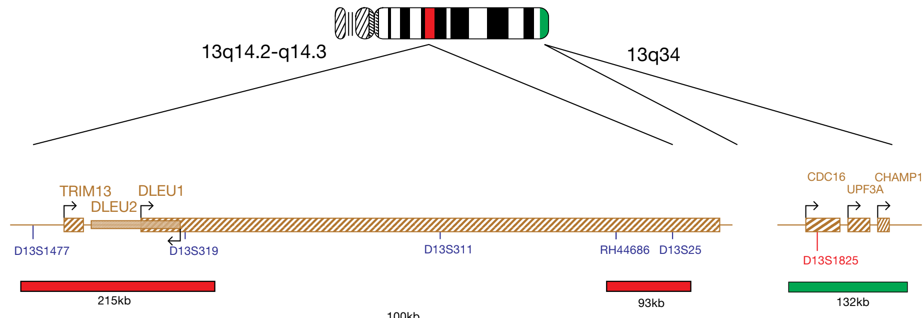

CMP-H001 v003.00

D13S319 *Plus*

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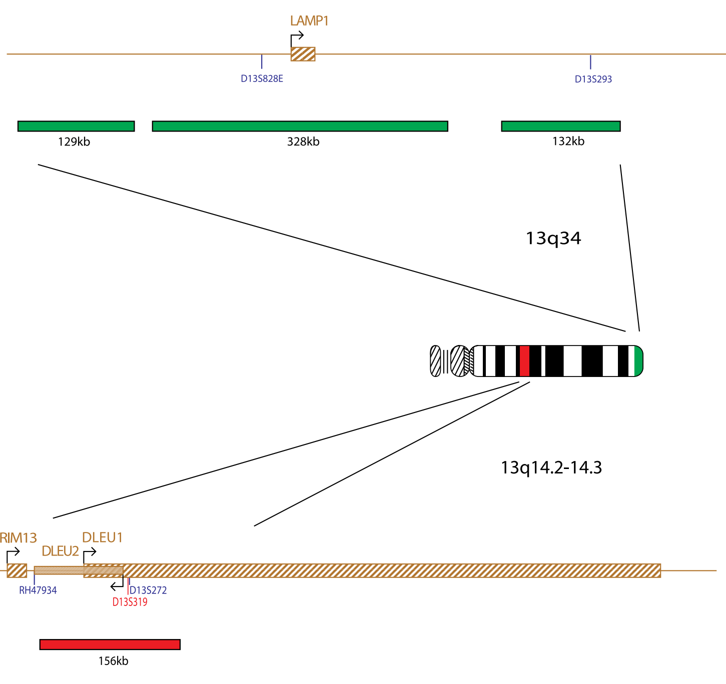

CMP-H079 v004.00

100kb

D13S25

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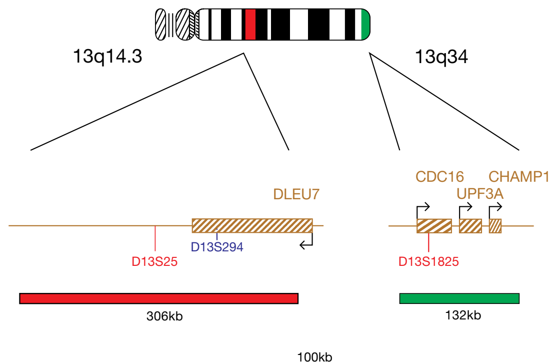

CMP-H016 v004.00

100kb

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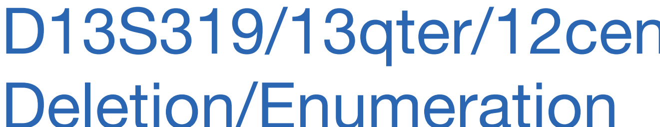
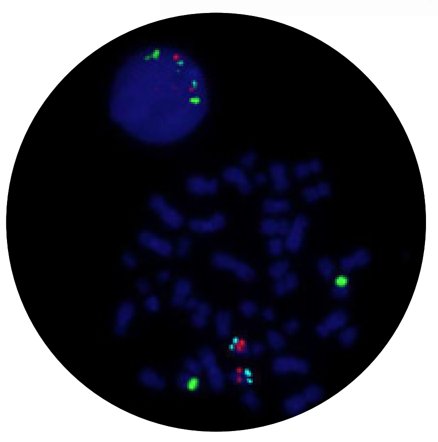
Cat. No. **LPH 066-S** (5 tests)
Cat. No. **LPH 066** (10 tests)



D13S319/13qter/12cen Deletion/Enumeration



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Deletions affecting band 13q14 and trisomy of chromosome 12 are common events in chronic lymphocytic leukaemia (CLL).

Deletions affecting 13q14 are also the most frequent structural genetic aberrations in chronic lymphocytic leukaemia (CLL)[1,2,3]. This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients[4]. The survival rate has been shown to be similar for the two groups[5]. Patients with 13q14 deletions are classified as very low risk, in the absence of any other genetic lesions[6].

Two non-coding RNA genes, DLEU1 (*deleted in lymphocytic leukemia 1*) and DLEU2 (*deleted in lymphocytic leukemia 2*), plus the genetic marker D13S319, span the pathogenic critical region of 13q14[7]. DLEU1 is considered to be the most likely CLL-associated candidate tumour suppressor gene within the 13q14 region[8].

Trisomy 12 is a recurrent abnormality in CLL, seen in 20% of the cases[9] and often appears as the unique cytogenetic aberration (40-60% of cases with trisomy 12)[2]. Patients with trisomy 12 are classified as low-risk in the absence of any other genetic lesions[6].

REFERENCES

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5. Van Dyke DL *et al*., Br J Haematology 2009;148:544-50
6. Rossi *et al*., Blood 2013;121(8):1403-1412
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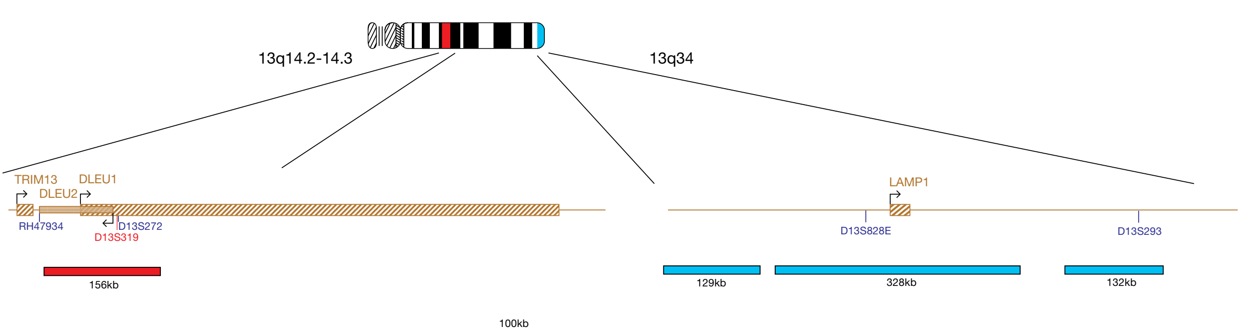
CMP-H074 v001.00



CMP-H073 v003.00

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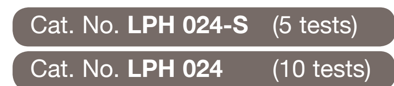
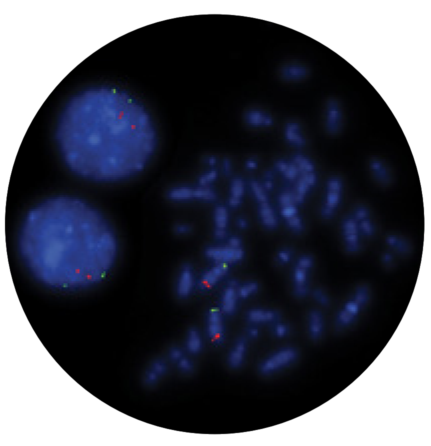


Del(5q) Deletion



Deletions of the long arm of chromosome 5 are one of the most common karyotypic abnormalities in myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) with myelodysplasia related changes[1,2].

A subset of patients with del(5q) as a sole cytogenetic abnormality has a consistent set of clinical features, termed the 5q- syndrome[1]. This clinical entity with <5% blasts has a more favourable prognosis and responds to treatment with lenalidomide. However, patients with del(5q) associated with other cytogenetic abnormalities or with excess blasts have an inferior survival[2,3].

Two chromosomal regions have been mapped on chromosome 5q in MDS. One common deleted region, at 5q33, is associated with the 5q-syndrome. Another, more proximal region, located at 5q31, has been linked to a more aggressive form of MDS and AML and is often accompanied by additional cytogenetic abnormalities and a poorer prognosis[1,3,4,].

The Cytocell del(5q) probe will detect deletions of EGR1 (*early growth response 1*), a tumour suppressor gene at 5q31.2 EGR1 has been shown to act through haploinsufficiency to initiate the development of MDS/AML[5].

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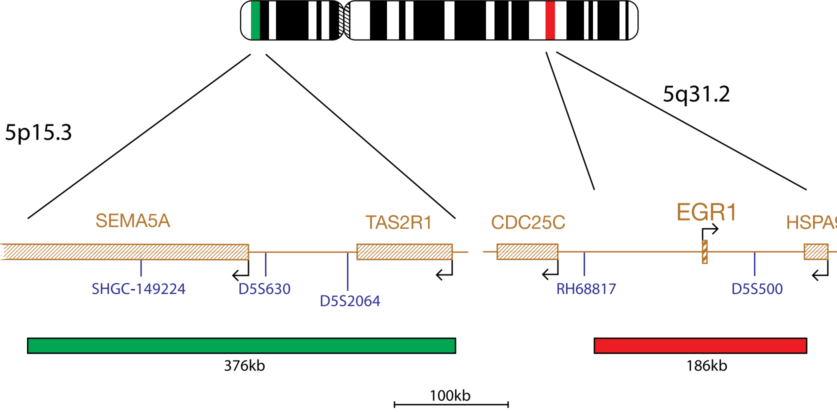

CMP-H017 v007.00

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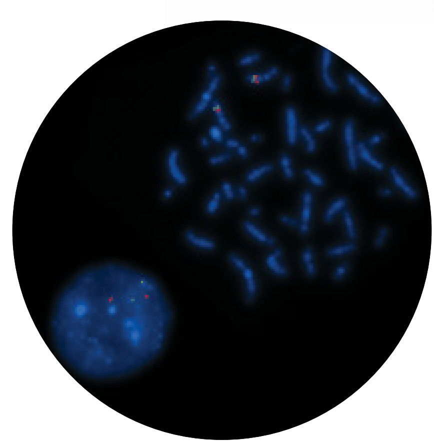
Del(7q) Deletion



Monosomy of chromosome 7 and deletions of the long arm of chromosome 7 are recognised recurrent chromosomal aberrations frequently seen in myeloid disorders.

Monosomy 7 and del(7q) are seen in a number of myeloid disorders, including myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), and juvenile myelomonocytic leukaemia (JMML)[1]. Furthermore, it occurs in MDS and AML that develop in patients with constitutional disorders (eg, Fanconi anaemia, Kostmann syndrome, neurofibromatosis type 1, and familial monosomy 7)[2]. The presence of monosomy 7 or del(7q) as karyotypic changes are associated with a poorer outcome in myeloid malignancies[1,3].

Deletions of chromosome 7 are typically large with heterogeneity in the breakpoints in myeloid diseases, making it difficult to map the common deleted regions (CDRs). It is highly likely that multiple tumour suppressor genes on chromosome 7 cooperate in leukaemogenesis[4]. Two CDRs have been previously reported: one at 7q22 and the other on 7q31-q36[2,5], which are both targeted by this probe set.

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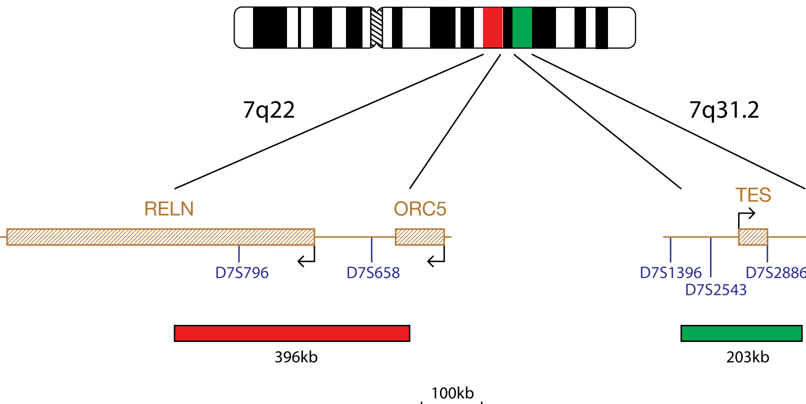

CMP-H018 v006.00

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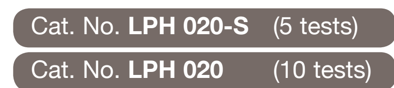
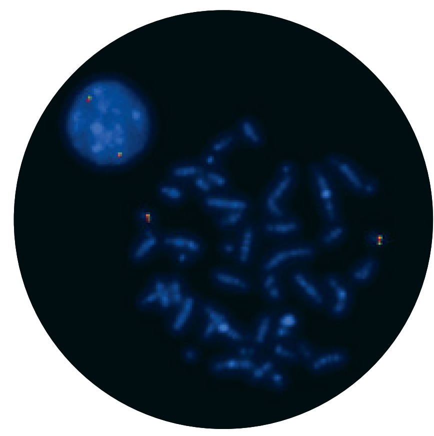


Del(20q) Deletion



Deletions of the long arm of chromosome 20 are a common chromosomal abnormality associated with myeloid malignancies, in particular myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML)[1].

Deletion of the long arm of chromosome 20 [del(20q)] is observed in 10% of patients with polycythemia vera (PV) and in other MPNs[2]. Additionally it can be seen in 4% of MDS cases and in 1-2% of AML cases[2]. The prognosis for MDS where del(20q) is the sole abnormality is good; however, the presence of secondary abnormalities may be indicative of disease progression[3].

FISH is particularly useful in confirming the presence and extent of the abnormality in poor cytogenetic sample preparations.

Potential target genes have been investigated in the region of overlap between the AML/MDS and MPD common deleted region at band 20q12. Five genes were expressed in both bone marrow and CD34+ cells. Of these genes, three were previously identified: L3MBTL1 regulates chromatin structure during mitosis; SRSF6 encodes a serine rich protein important to regulation of alternative splicing of mRNA; and MYBL2, a member of the MYB transcription factor family, is involved in cell cycle control[2,4,5].

**

REFERENCES

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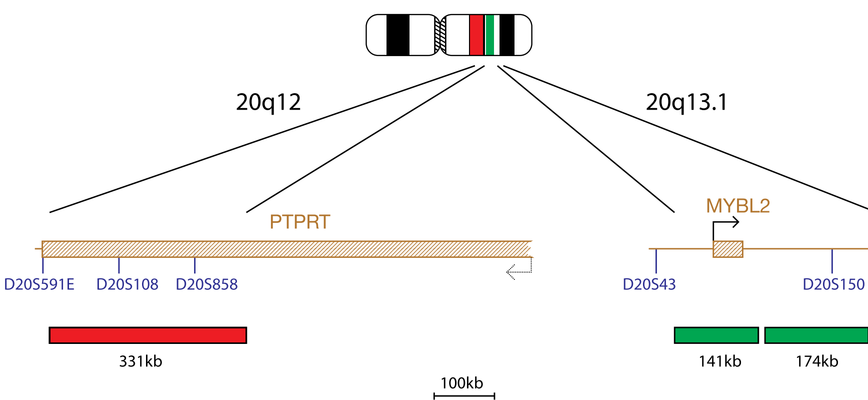

CMP-H019 v006

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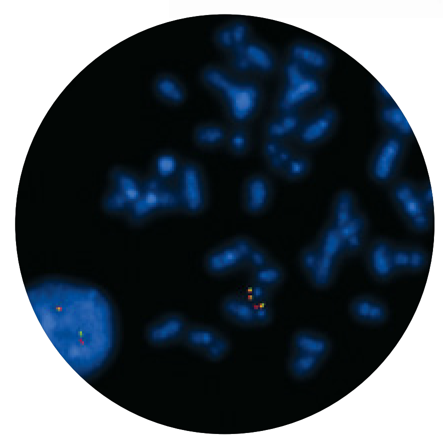
Cat. No. **LPH 019-S** (5 tests)
Cat. No. **LPH 019** (10 tests)

E2A (TCF3) Breakapart



The TCF3 (*transcription factor 3*) gene is located at 19p13.3. Translocations involving TCF3 are some of the most common rearrangements in childhood B-cell acute lymphoblastic leukaemia (ALL)[1,2].

Two of the main TCF3 partners are PBX1 (*PBX homeobox 1*) at 1q23.3 and HLF (*HLF transcription factor, PAR bZIP family member*) at 17q22. These become fused to TCF3 as a result of the t(1;19)(q23;p13) and t(17;19)(q22;p13) translocations, forming the TCF3-PBX1 and TCF3-HLF fusion genes, respectively. A rare cryptic inversion, inv(19)(p13;q13), has been reported to fuse TCF3 to TFPT (*TCF3 fusion partner*) resulting in the TCF3-TFPT fusion gene[1].

The t(1;19)(q23;p13) is the most common TCF3 rearrangement, being present in around 6% of childhood B-ALL[1,2]. According to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia, B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13); TCF3-PBX1 is recognised as a distinct disease entity[2]. The functional fusion gene resides at chromosome 19. An unbalanced form of this translocation has been reported, with loss of der(1)[1,2]. Detection of the E2A-PBX1 fusion by molecular methods, such as FISH, is important, as a subset of B-ALLs has a karyotypically identical t(1;19) that involves neither TCF3 nor PBX1. E2A-PBX1 positive leukaemia was historically associated with a poor outcome, though modern intensive therapies have overcome this[1,2,4].

The t(17;19)(q22;p13.) is a rare translocation that is present in around 1% of precursor B-ALL cases[1]. TCF3-HLF positive leukaemia is associated with adverse prognosis[3,4].

**

REFERENCES

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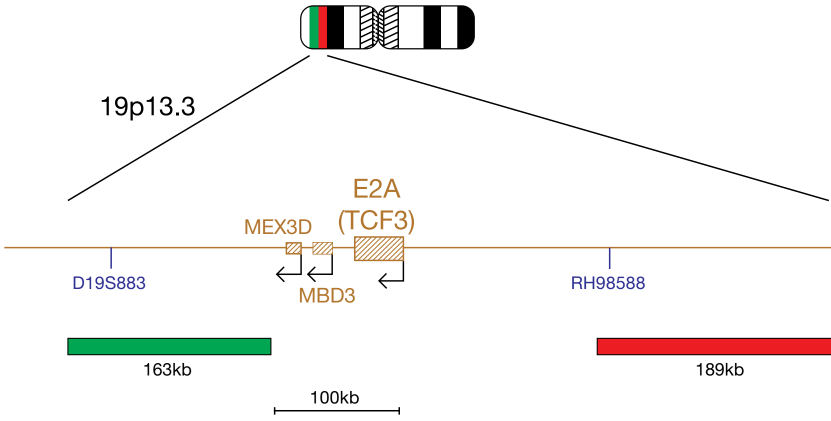

CMP-H020 v002

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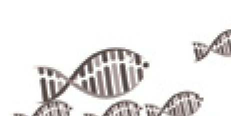
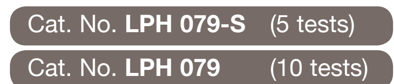
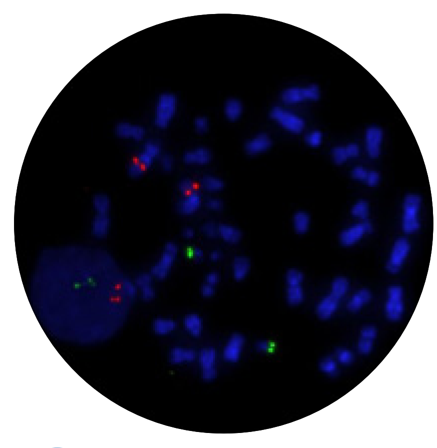




E2A (TCF3)/PBX1 Translocation, Dual Fusion



The TCF3 (*transcription factor 3*) gene is located at 19p13.3 and PBX1 (*PBX homeobox 1*) at 1q23.3. Trans-locations involving TCF3 are some of the most common rearrangements in childhood B-cell acute lymphoblastic leukaemia (ALL)[1,2].

Two of the main TCF3 partners are PBX1 at 1q23.3 and HLF at 17q22. These become fused to TCF3 as a result of the t(1;19)(q23;p13) and t(17;19)(q22;p13) translocations, forming the TCF3-PBX1 and TCF3-HLF fusion genes, respectively. A rare cryptic inversion, inv(19)(p13;q13), has been reported to fuse TCF3 to TFPT (*TCF3 fusion partner)*, resulting in the TCF3-TFPT fusion gene[1].

UK and European best practice guidelines both suggest that when a TCF3 rearrangement is identified in B-cell ALL, it is important to distinguish between t(17;19)(q22;p13) and t(1;19)(q23;p13) as the former translocation is associated with adverse prognosis[3,4].

**

REFERENCES

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2. Swerdlow *et al*.,editors, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France, IARC:2008
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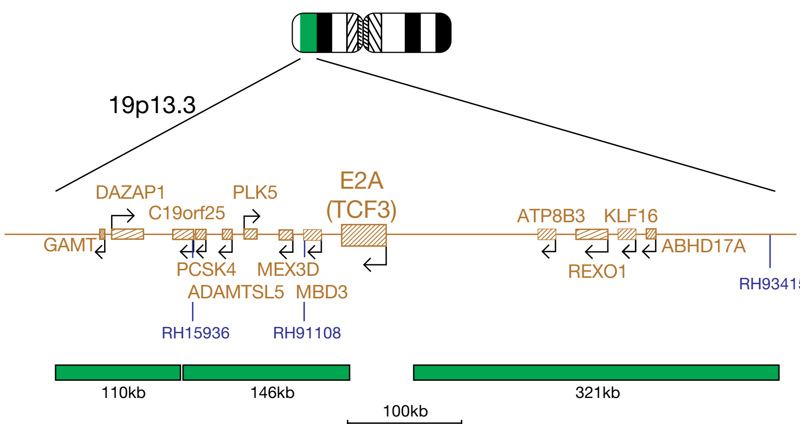
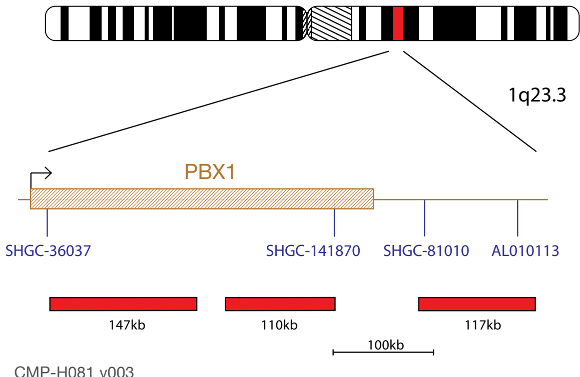


CMP-H080 v001



CMP-H081 v003

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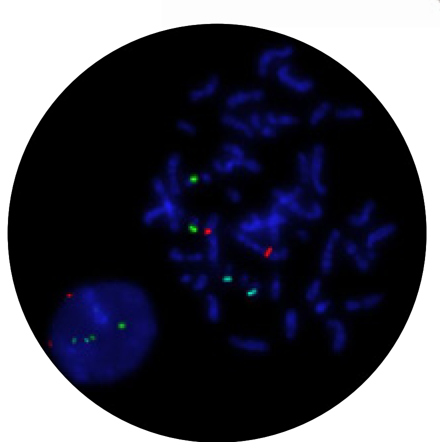
E2A/PBX1 *Plus* Translocation, Dual Fusion



The TCF3 (*transcription factor 3*) gene is located at 19p13.3, PBX1 (*pre-B-cell leukemia homeobox 1*) gene is located at 1q23.3 and HLF (*HLF transcription factor, PAR bZIP family member*) at 17q22. Translocations involving TCF3 are some of the most common rearrangements in childhood B-cell acute lymphoblastic leukaemia (ALL)[1,2].

PBX1 and HLF become fused to TCF3 as a result of the t(1;19)(q23;p13) and t(17;19)(q22;p13) translocations, forming the TCF3-PBX1 and TCF3-HLF fusion genes, respectively. A rare cryptic inversion, inv(19)(p13;q13), has been reported to fuse TCF3 to TFPT (*TCF3 fusion partner*), resulting in the TCF3-TFPT fusion gene[1].

**

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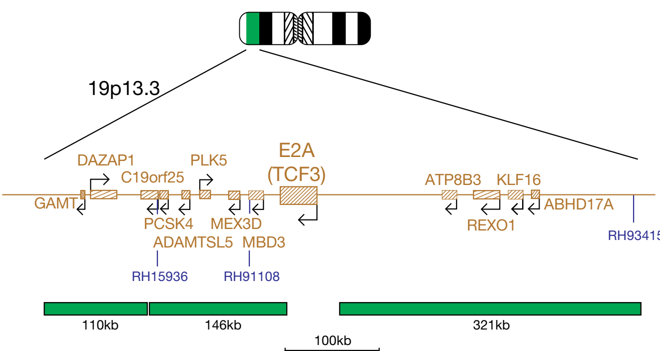

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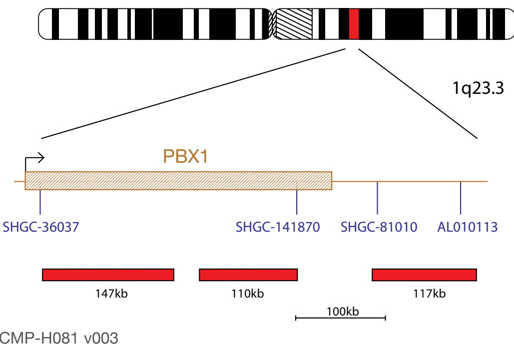
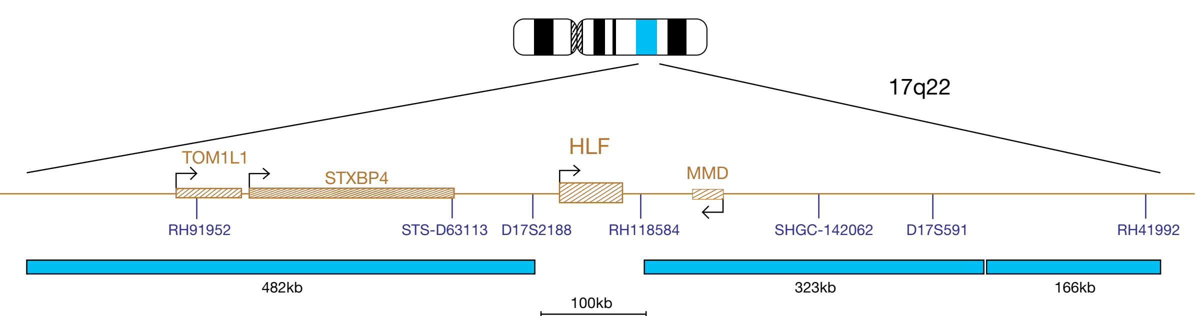


CMP-H081 v003



CMP-H082 v002

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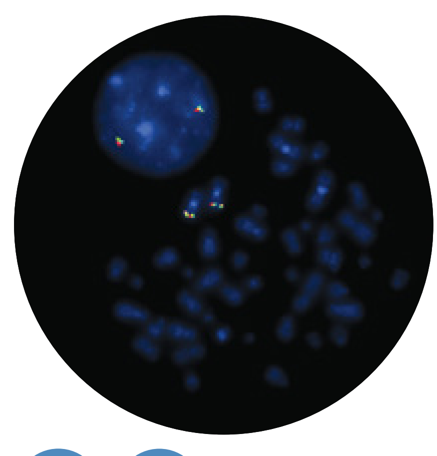
EVI1 (MECOM) Breakapart



The MECOM (*MDS1 and EVI1 complex locus*) oncogene at 3q26.2 is often rearranged in haematological malignancies of myeloid origin.

MECOM encodes a zinc finger protein that is inappropriately expressed in the leukaemic cells of between 2-5% of AML and MDS patients[1]. This deregulated expression is often due to a chromosomal rearrangement involving 3q26.2, with the two most common aberrations being the t(3;3)(q21;q26.2) and inv(3)(q21q26.2)[1]. The breakpoints for the translocations and inversions vary considerably. Inversion breakpoints are found centromeric to, and including, the MECOM gene and cover about 600kb. The majority of breakpoints in 3q26.2 translocations are telomeric to the MECOM gene and cover a region including the telomeric end of the MDS1 gene and the MYNN gene[2].

Chromosome rearrangements involving the 3q26.2 region are associated with myeloid malignancies, aberrant expression of MECOM gene, an unfavourable prognosis and an aggressive clinical course[2].

AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) is a recognised disease entity according to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia. This is a transformed or *de novo* AML with a very aggressive clinical course and aberrations that involve MECOM at 3q26.2 and RPN1 (*ribophorin I*) at 3q21[3].

MECOM has also been shown to be rearranged in therapy-related disease via the t(3;21)(q26.2;q22) translocation, resulting in a MECOM-RUNX1 fusion[3,4].

MECOM rearrangements are very heterogeneous and may be difficult to detect by conventional cytogenetics, making FISH a useful tool for their detection.

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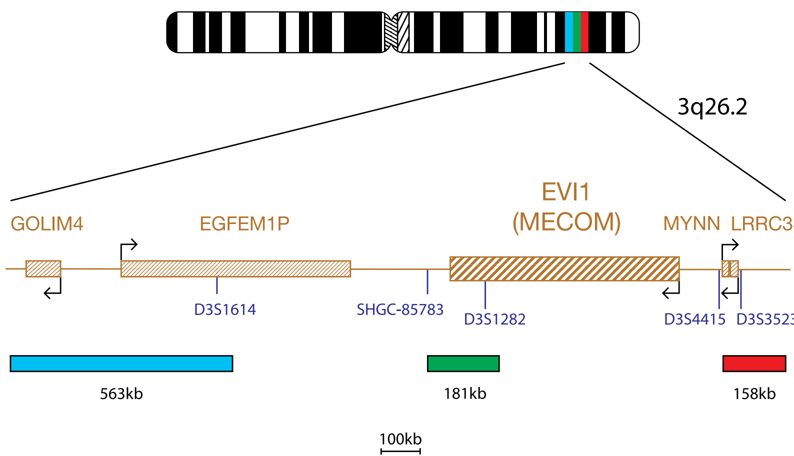

CMP-H021 v008

IVD: *In Vitro* Diagnostic Medical Device

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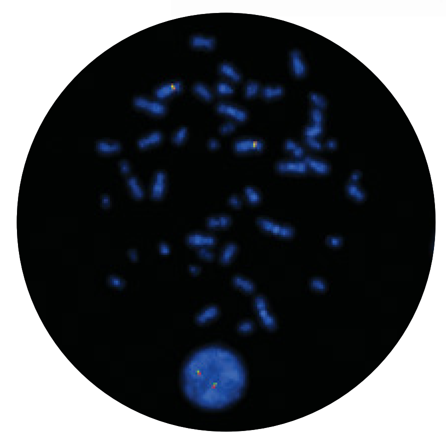
FIP1L1/CHIC2/PDGFRA Deletion/Fusion



Deletion of CHIC2 (*cysteine rich hydrophobic domain 2*) at 4q12 results in the fusion of FIP1L1 (*factor interacting with PAPOLA and CPSF1*) at 4q12 with PDGFRA (*platelet derived growth factor receptor alpha*) at 4q12 producing a tyrosine kinase which transforms haematopoietic cells[1].

In the 2008 World Health Organization (WHO) classification of myeloid neoplasms and acute leukaemia, a new subgroup of myeloid neoplasms was introduced: *Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB or FGFR1*. These neoplasms constitute three specific disease groups, with some shared features[1].

The most common myeloproliferative neoplasms (MPN) showing PDGFRA rearrangements are those with FIP1L1-PDGFRA fusions. These MPNs present as chronic eosinophilic leukaemia (CEL) or, more rarely, as acute myeloid leukaemia (AML). As this abnormality is cytogenetically cryptic, FISH provides a useful tool for the detection of the fusion[1,2].

Patients with the fusion benefit from treatment with tyrosine kinase inhibitors (TKIs). The diagnosis of the fusion gene can therefore lead to therapeutic choices for the patient[1,2].

**

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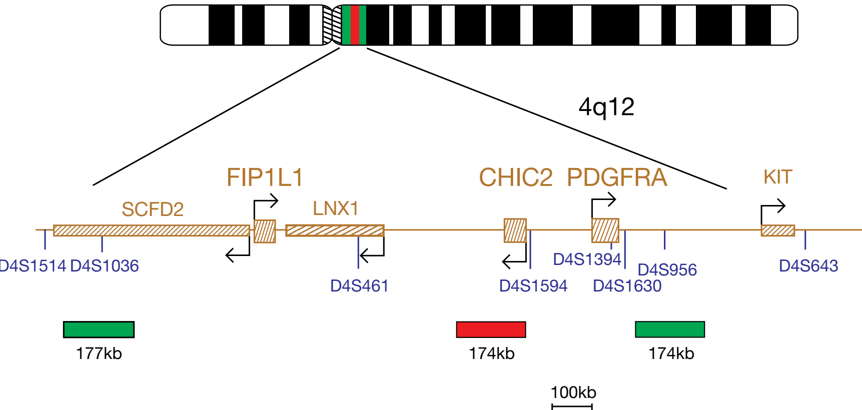

CMP-H022 v003

IVD: *In Vitro* Diagnostic Medical Device
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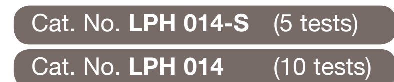


IGH Breakapart*

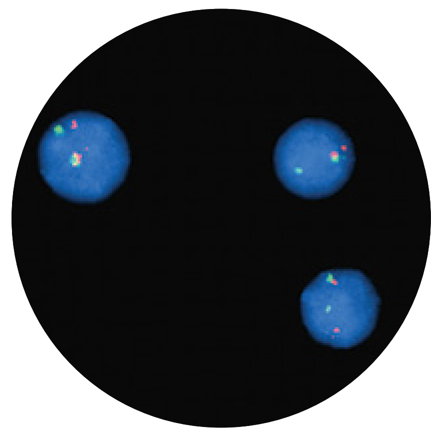
Recurrent rearrangements involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.3 with a wide range of partner genes are seen in lymphomas and haematological malignancies[1].

A t(8;14)(q24;q32) translocation, involving IGH and the MYC gene at 8q24, is frequently seen in Burkitt lymphoma[2] and diffuse large B-cell lymphoma (DLBCL)[3]. Other rearrangements frequently reported in B-cell lymphoma include: the t(14;18)(q32;q21) translocation, involving IGH and the BCL2 gene, seen in both follicular lymphoma and DLBCL[4]; and the t(11;14)(q13;q32) involving IGH and the CCND1 gene, which is the hallmark of mantle cell lymphoma (MCL)[5].

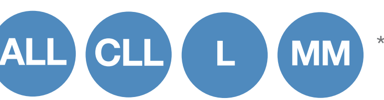
IGH rearrangements with a number of different gene partners are a frequent finding in patients with multiple myeloma, including: t(4;14)(p16;q32) translocations involving IGH with FGFR3 and NSD2; t(6;14)(p21;q32) translocations involving IGH and CCND3; t(11;14)(q13;q32) translocations involving IGH and CCND1; t(14;16)(q32;q23) translocations involving IGH and MAF, and t(14;20)(q32;q12) translocations involving IGH and MAFB[6,7].

IGH rearrangements are also reported as recurrent abnormalities in patients with lymphoplasmacytic lymphoma (LPL), chronic lymphocytic leukaemia (CLL), extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type and acute lymphoblastic leukaemia (ALL)[8].

The breakapart design for this probe set allows the detection of rearrangements of the IGH region, regardless of partner gene or chromosome involved.



IGH-rearranged sample



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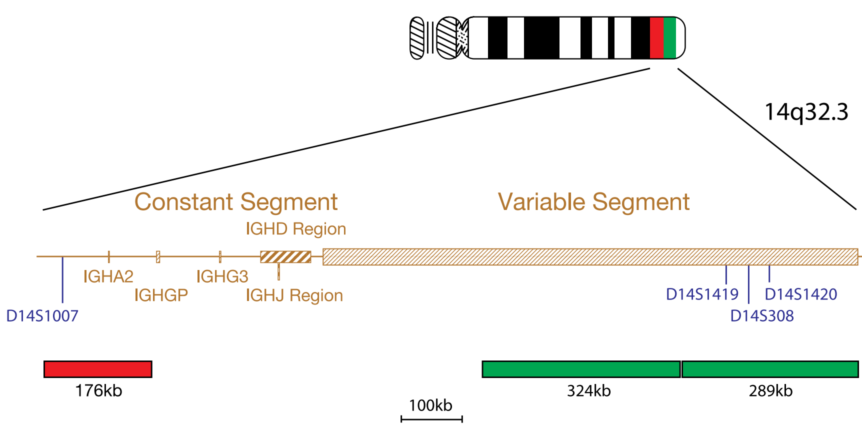

CMP-H023 v003

*A similar product is also available in the Haematopathology range, refer to page 80.

IVD: *In Vitro* Diagnostic Medical Device

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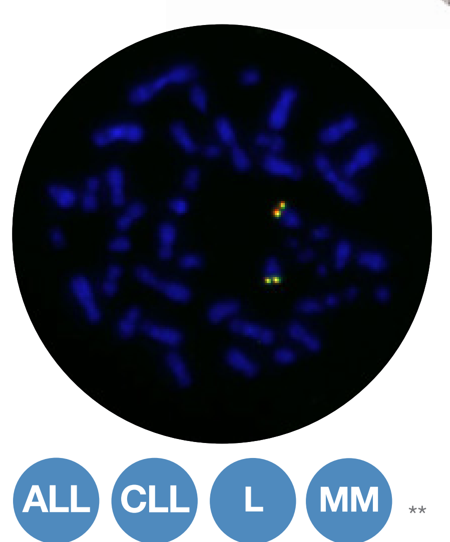
Cat. No. **LPH 070-S** (5 tests)
Cat. No. **LPH 070** (10 tests)

IGH *Plus* Breakapart*



ALL CLL L MM **

Recurrent rearrangements involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.3 with a wide range of partner genes are seen in lymphomas and haematological malignancies[1].

A t(8;14)(q24;q32) translocation, involving IGH and the MYC gene at 8q24, is frequently seen in Burkitt lymphoma[2] and diffuse large B-cell lymphoma (DLBCL)[3]. Other rearrangements frequently reported in B-cell lymphoma include: the t(14;18)(q32;q21) translocation, involving IGH and the BCL2 gene, seen in both follicular lymphoma and DLBCL[4]; and the t(11;14)(q13;q32) involving IGH and the CCND1 gene, which is the hallmark of mantle cell lymphoma (MCL)[5].

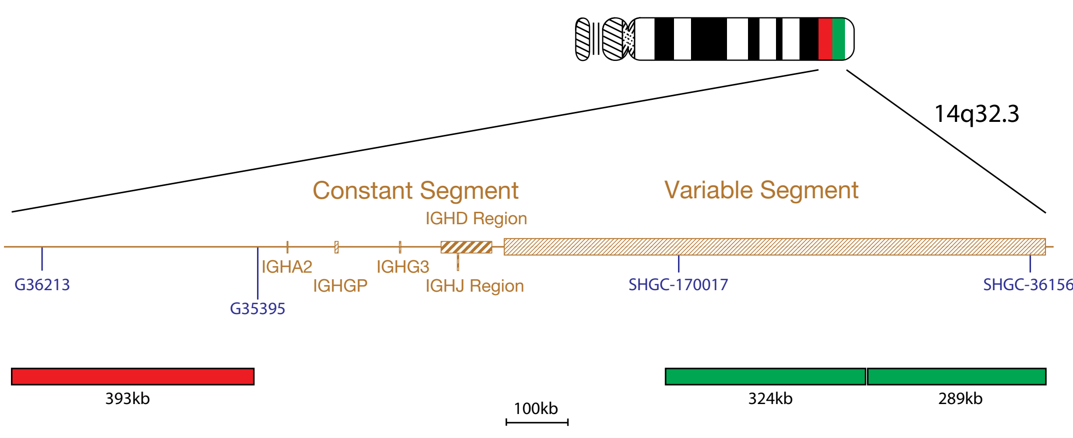
IGH rearrangements with a number of different gene partners are a frequent finding in patients with multiple myeloma, including: t(4;14)(p16;q32) translocations involving IGH with FGFR3 and NSD2; t(6;14)(p21;q32) translocations involving IGH and CCND3; t(11;14)(q13;q32) translocations involving IGH and CCND1; t(14;16)(q32;q23) translocations involving IGH and MAF, and t(14;20)(q32;q12) translocations involving IGH and MAFB[6,7].

IGH rearrangements are also reported as recurrent abnormalities in patients with lymphoplasmacytic lymphoma (LPL), chronic lymphocytic leukaemia (CLL), extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type and acute lymphoblastic leukaemia (ALL)[8].

The breakapart design for this probe set allows the detection of rearrangements of the IGH region, regardless of partner gene or chromosome involved.

REFERENCES

1. Gozzetti A, *et al*. Cancer Res.2002 Oct 1;62(19):5523-7
2. Ferry JA. Oncologist 2006 Apr;11(4):375-83
3. Li S, *et al*. Mod Pathol. 2012 Jan;25(1):145-56
4. Snuderl M, *et al*. Am J Surg Pathol. 2010 Mar;34(3):327-40
5. Vose JM. Am J Hematol. 2013;88(12):1082-8
6. Bergsagel PL, *et al*. Proc Natl Acad Sci. 1996;93(24):13931-6
7. Sawyer JR. Cancer Genet. 2011 Jan;204(1):3-12
8. Swerdlow SH, *et al*, (eds,) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, Lyon, France, 4th edition, IARC,2017



CMP-H075 v002

***A similar product is also available within the Haematopathology range to page 80.**

IVD: *In Vitro* Diagnostic Medical Device
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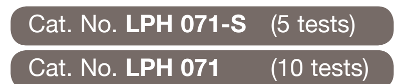
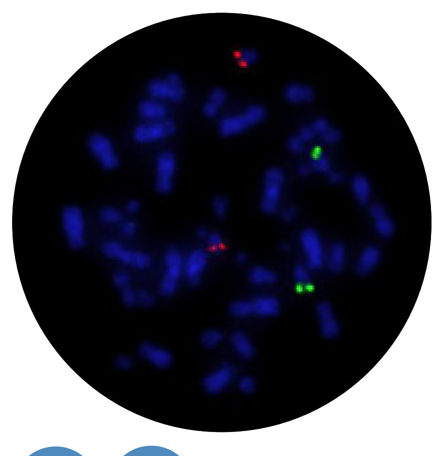


IGH/BCL2 *Plus* Translocation, Dual Fusion*



The t(14;18)(q32;q21) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.3 and the BCL2 (*BCL2 apoptosis regulator*) gene at 18q21.33 is a recognised recurrent abnormality seen in B-cell malignancies.

IGH-BCL2 rearrangements are observed in 70-95% of follicular lymphoma (FL) cases and 20-30% of diffuse large B-cell lymphoma (DLBCL)[1]. Presence of the t(14;18) translocation in DLBCL is a predictor of outcome and has a poor prognostic effect[2]. BCL2 translocations have also been implicated in chronic B-cell lymphoproliferative disease (CLPD) and also occur occasionally in chronic lymphocytic leukaemia (CLL)[3].

L CLL **

REFERENCES

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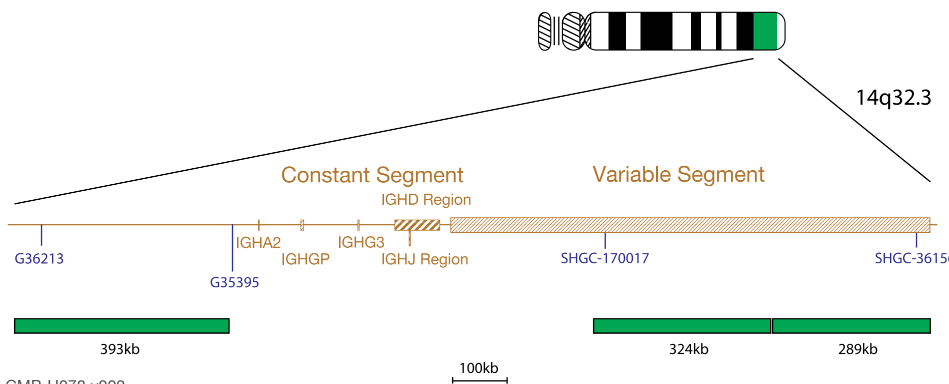

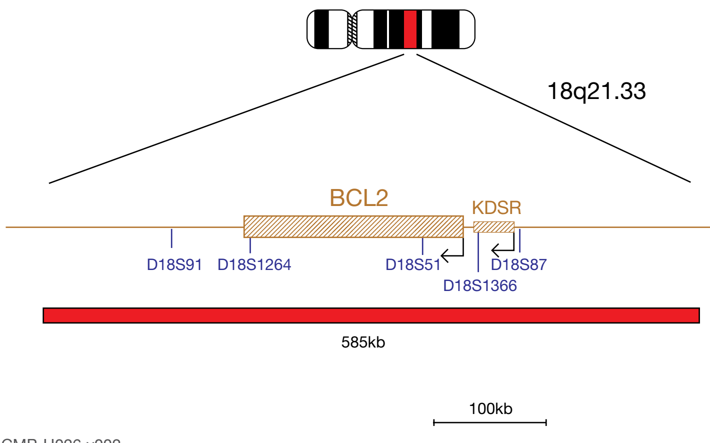

***A similar product is also available within the Haematopathology range, refer to page 81.**

IVD: *In Vitro* Diagnostic Medical Device

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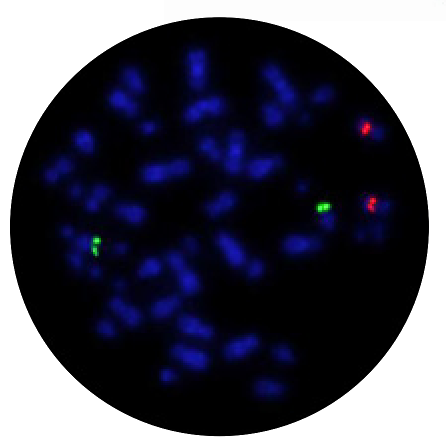
Cytocell aquarius

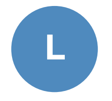
Cat. No. **LPH 072-S** (5 tests)
Cat. No. **LPH 072** (10 tests)

IGH/CCND1 *Plus* Translocation, Dual Fusion*



The t(11;14)(q13;q32) translocation involving CCND1 (*cyclin D1*) gene at 11q13.3 and the IGH (*immunoglobulin heavy locus*) gene at 14q32.33 is associated with mantle cell lymphoma.

The t(11;14)(q13;q32) rearrangement involving CCND1 and IGH is considered the hallmark of mantle cell lymphoma (MCL)[1], the presence of which can be used to aid in the differential diagnosis of CD5+ B-cell lymphoproliferative disorders[2].



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REFERENCES

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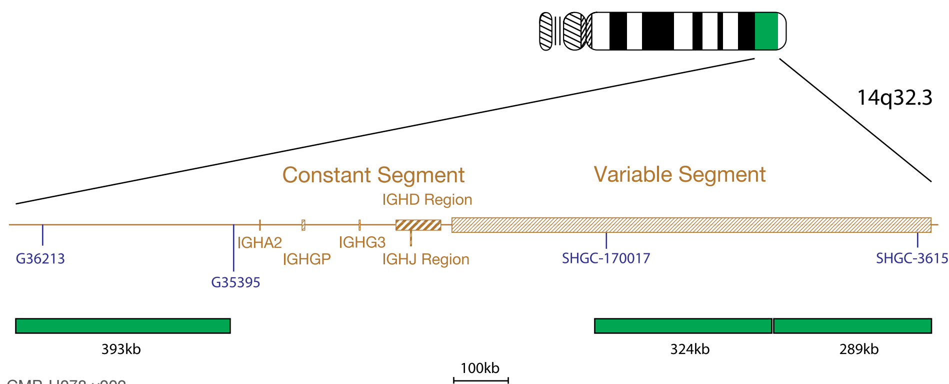

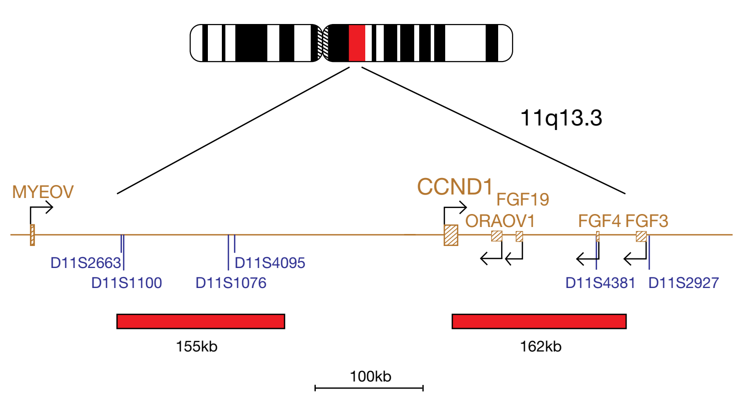

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IVD: *In Vitro* Diagnostic Medical Device

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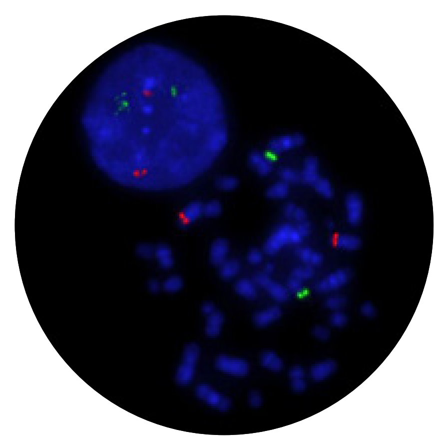
IGH/CCND3 *Plus* Translocation, Dual Fusion



The CCND3 (*cyclin D3*) gene is located at 6p21.1 and IGH (*immunoglobulin heavy locus*) at 14q32.3.

Approximately 50-60% of multiple myeloma (MM) cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1) and FGFR3, CCND3, MAF or MAFB[1].

The t(6;14)(p21;q32) translocation is a recurrent translocation seen in 4% of cases of MM[2].

CCND3 has been identified as a putative oncogene that is dysregulated as a consequence of the t(6;14)(p21;q32) translocation[2]. The translocation appears to be mediated by an error in IgH switch recombination as it has been shown that in KMM-1 cell lines, the translocation disrupts a switch sequence in this region and results in juxtaposition of CCND3 with the IGH promoter, thus elevating the levels of CCND3 expression[2]. It is thought that this mechanism is similar in all cases of IGH translocation. Most breakpoints appear to be clustered in a region that is fewer than 200kb centromeric to CCND3[2].

CCND3-IGH translocations are also reported in a variety of other B-cell malignancies, including plasma cell leukaemia, diffuse large B-cell lymphoma (DLBCL) and splenic lymphoma with villous lymphocytes (SLVL)[3].

**

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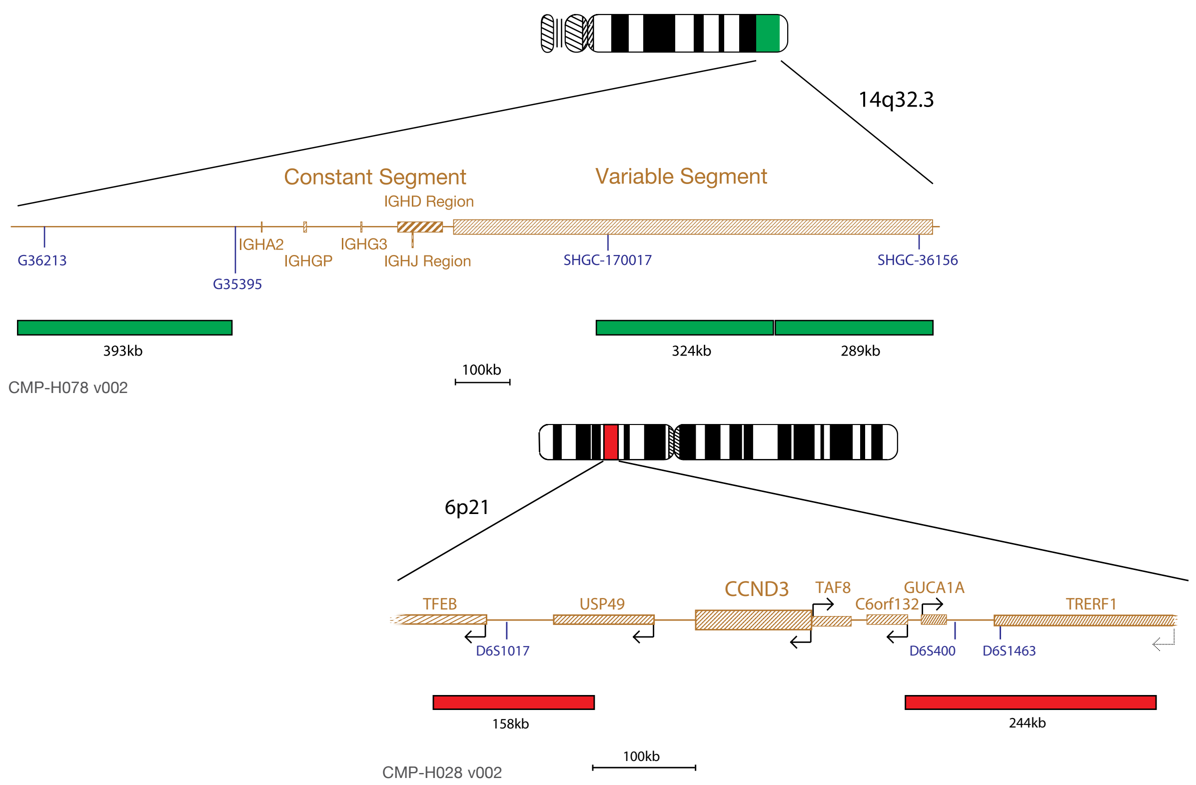

IVD: *In Vitro* Diagnostic Medical Device

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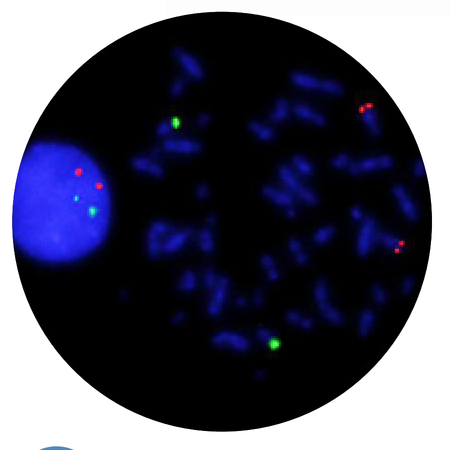
IGH/cMYC (MYC) *Plus* Translocation, Dual Fusion*



The t(8;14)(q24;q32) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.3 and the MYC (*MYC proto-oncogene, bHLH transcription factor*) oncogene at 8q24 is a recognised recurrent abnormality commonly seen in patients with B-cell malignancy.

IGH-MYC rearrangements are detected in up to 85% of cases of Burkitt lymphoma at diagnosis[1]. They are also seen in diffuse large B-cell lymphoma (DLBCL)[2], multiple myeloma and plasmablastic lymphoma[3,4].

In an IGH-MYC rearrangement the translocation breakpoints on chromosome 14 are clustered to a narrow region 5' to the intron enhancer of the immunoglobulin heavy chain, whereas the breakpoints on chromosome 8 can occur more than 340kb upstream of MYC, with no preferential site[5]. The translocation brings MYC into close proximity to the IGH enhancer and results in the up-regulation of MYC. Over-expression of the transcription factor stimulates gene amplification, resulting in uncontrolled cell proliferation[6].

**

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14q32.3
Constant Segment
Variable Segment
IGHD Region
G36213
IGHA2
IGHGP
IGHG3
IGHJ Region
SHGC-170017
SHGC-36156
G35395
393kb
324kb
289kb
100kb

CMP-H078 v002

8q24.21
POU5F1B
MYC
CASC8
PVT1
D8S1153 D8S1128
D8S490 D8S1087 D8S1644
D8S1980 D8S1720
220kb
186kb
100kb

CMP-H029 v003

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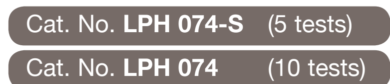
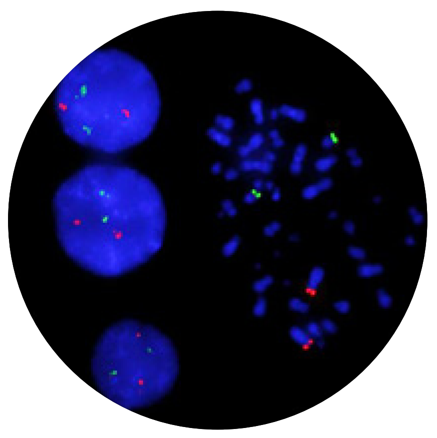


IGH/FGFR3 *Plus* Translocation, Dual Fusion



The FGFR3 (*fibroblast growth factor receptor 3*) gene is located at 4p16.3 and IGH (*immunoglobulin heavy locus*) at 14q32.33.

Approximately 50-60% of multiple myeloma (MM) cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1), and FGFR3, CCND3, MAF or MAFB[1].

The t(4;14)(p16.3;q32.3) translocation is a recurrent translocation seen in 15% of MMs[2,3].

The translocation results in the dysregulation of two genes at 4p16; WHSC1 (*Wolf-Hirschhorn syndrome candidate 1*) and FGFR3. The consequence of the translocation is increased expression of FGFR3 and WHSC1. The translocation can be unbalanced, with 25% of cases losing the derivative chromosome 14, associated with the loss of FGFR3 expression[2,3].

The majority of the breakpoints on chromosome 4 occur between FGFR3 and WHSC1. The breakpoint on chromosome 14 is almost exclusively in the switch region of constant genes. For the overexpression of both FGFR3 and WHSC1 the breakpoint on chromosome 14 must be located between the μ enhancer and the 3' IGH enhancers and between FGFR3 and WHSC1. As a consequence both derivative chromosomes contain an enhancer juxtaposed to an oncogene[4]. This t(4;14) translocation is often cytogenetically cryptic and was poorly described before the advent of FISH techniques. The translocation has been associated with poorer survival in MM patients[2,3].

**

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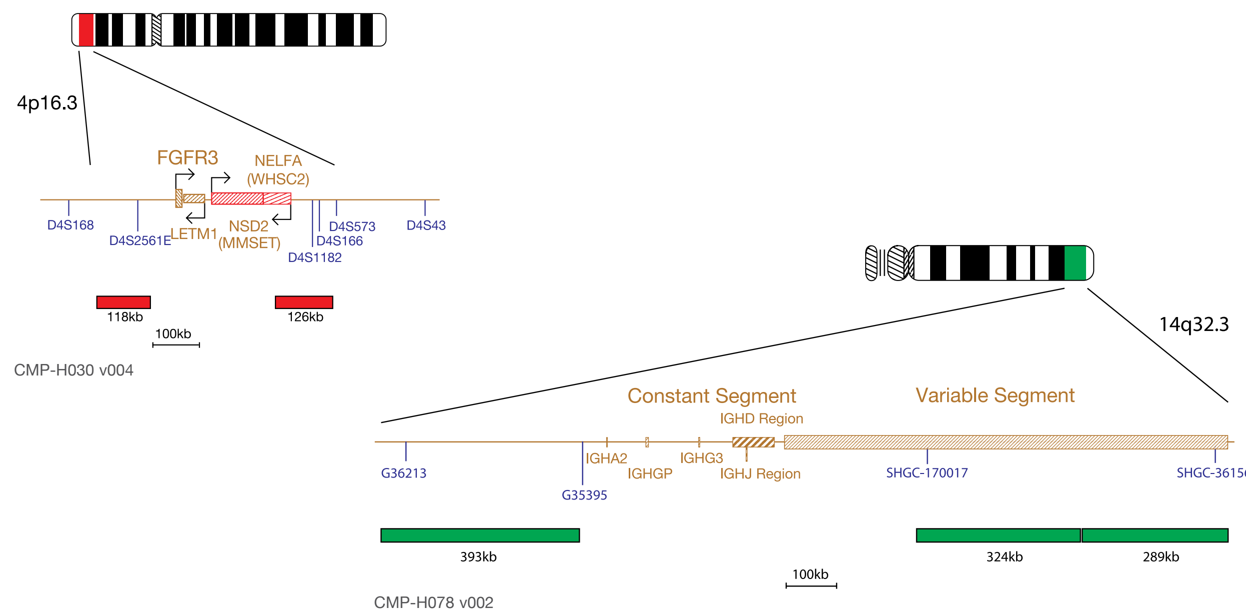

IVD: *In Vitro* Diagnostic Medical Device

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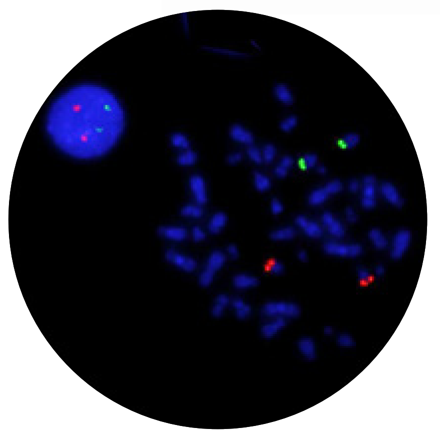
Cytocell aquarius

Cat. No. **LPH 108-S**	(5 tests)
Cat. No. **LPH 108**	(10 tests)

IGH/MAF *Plus* v2 Translocation/Dual Fusion



MAF (*MAF bZIP transcription factor*) gene is located at 16q23 and IGH (*immunoglobulin heavy locus*) at 14q32.3.

Approximately 50-60% of multiple myeloma (MM) cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1) and FGFR3, CCND3, MAF or MAFB[1]. The t(14;16)(q32.3;q23) translocation is a recurrent translocation seen in 2-10%of MMs[1].

The majority of the breakpoints occur within the last intron of WWOX (*WW domain containing oxidoreductase*), centromeric to MAF. These breakpoints have a dual impact of positioning the IGH enhancer near MAF and disrupting the WWOX gene[2]. Gene expression profiling of myeloma cell lines revealed that MAF caused transactivation of cyclin D2 (a promoter of cell cycle progression), thus enhancing proliferation of myeloma cells[3].

According to the literature, MM patients harbouring the t(14;16) appear to have a more aggressive clinical outcome[4,5].

**

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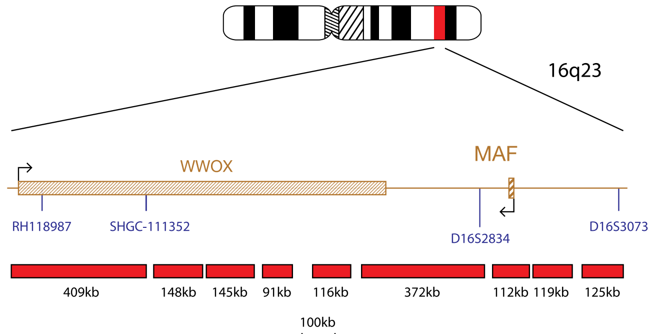
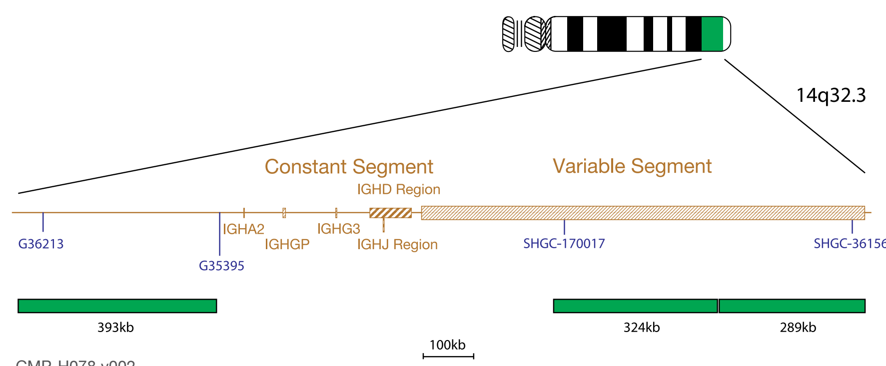


CMP-H139 v001



CMP-H078 v002

IVD: *In Vitro* Diagnostic Medical Device
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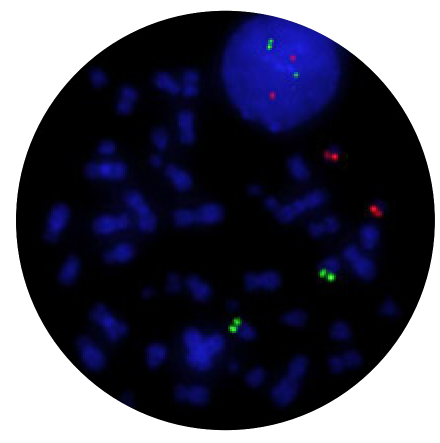
IGH/MAFB *Plus* Translocation, Dual Fusion



The MAFB (*MAF bZIP transcription factor B*) gene is located at 20q12 and IGH (*immunoglobulin heavy locus*) at 14q32.3.

Approximately 50-60% of multiple myeloma (MM) cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1) and FGFR3, CCND3, MAF or MAFB[1].

The t(14;20)(14q32;q12) translocation is a recurrent translocation seen in around 2% of MMs[2,3].

The reciprocal rearrangement brings a truncated form of the IGH μ-enhancer (Eμ, located between the joining (J) segments and the constant region of the IGH gene) in close contact with the MAFB gene[4]. The resultant fusion and the up-regulated transcription product has been shown to cause dysregulation of cyclin D2[1].

The prognostic outcome of t(14;20)(14q32;q12) is assumed to be the same as the t(14;16)(q32;q23)[3].

**

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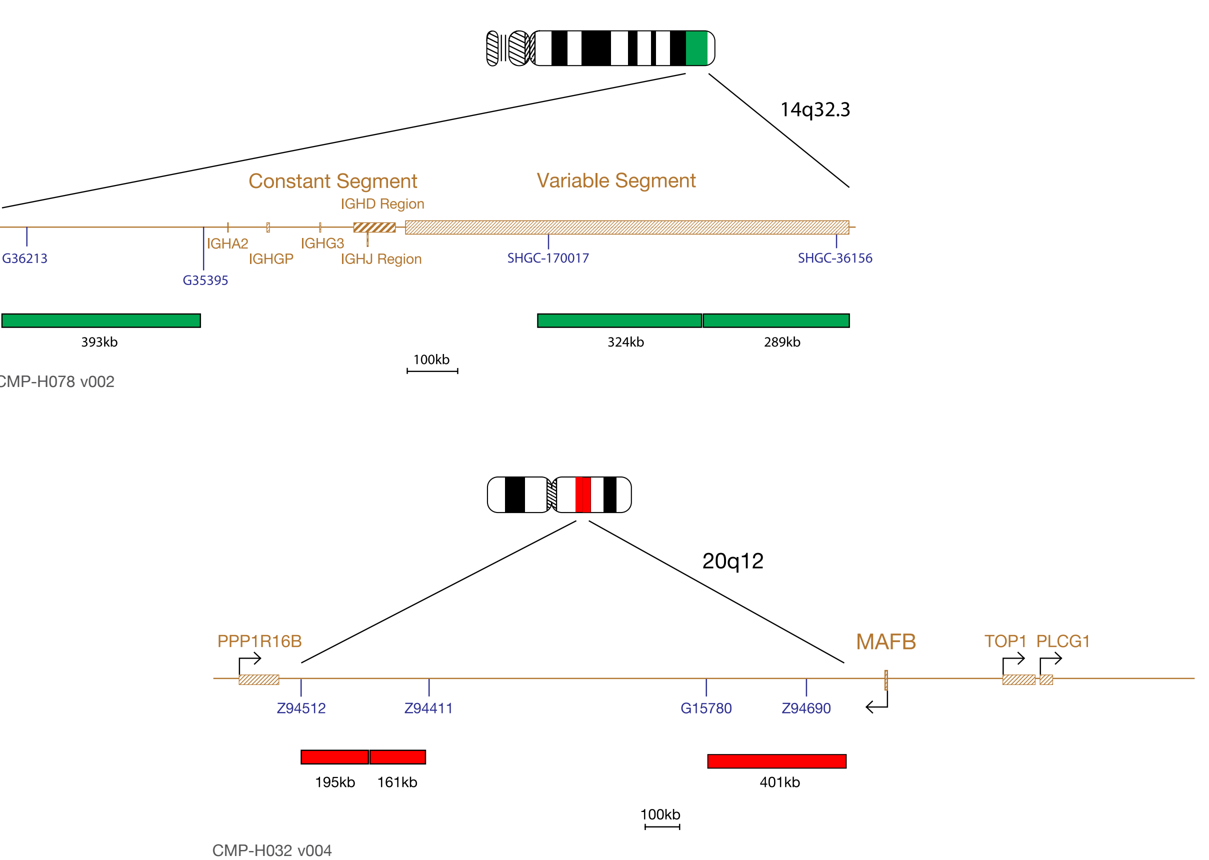

IVD: *In Vitro* Diagnostic Medical Device

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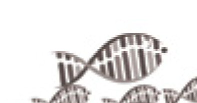
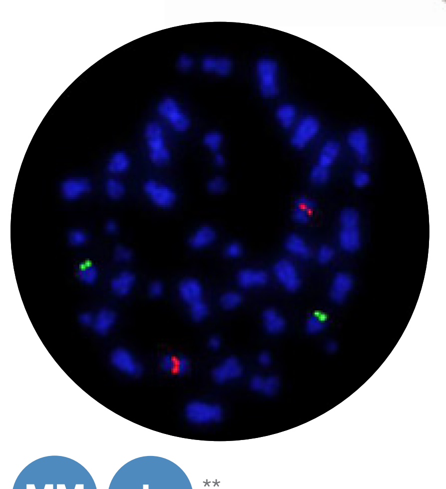


Cat. No. **LPH 078-S** (5 tests)
Cat. No. **LPH 078** (10 tests)

IGH/MYEOV *Plus* Translocation, Dual Fusion



The MYEOV (*myeloma overexpressed*) gene is located at 11q13.3 and IGH (*immunoglobulin heavy locus*) at 14q32.3.

Approximately 50-60% of multiple myeloma (MM) cases are associated with translocations involving IGH and one of several partners including CCND1, NSD2 (WHSC1) and FGFR3, CCND3, MAF or MAFB[1].

The t(11;14)(q13;q32.3) translocation is the most common translocation in MM, where it is seen in approximately 15% of cases [2,3].

Unlike mantle cell lymphoma (MCL), where the breakpoints are clustered in a 1kb region that is 120kb centromeric to the CCND1 gene[4], the breakpoints in MM cases are dispersed within a 360kb region between CCND1 and MYEOV at 11q13[5]. MYEOV is a putative oncogene, located 360kb centromeric to CCND1, which is thought to be activated in the translocation by becoming closely associated with IGH enhancers. In contrast to IGH rearrangements in other neoplasms, those found in MM have IGH breakpoints predominantly in the C/J region, which, in the case of MYEOV, brings the MYEOV gene under the control of the 3' Eα1 enhancer[5]. In CCND1 translocations by contrast, the Eμ enhancer controls CCND1 expression. MYEOV overexpression is a possible prognostic factor in MM[6].

The t(11;14)(q13;q32.3) is associated with a favourable outcome in most series and therefore is regarded as neutral with regard to prognosis[3].

MM L **

REFERENCES

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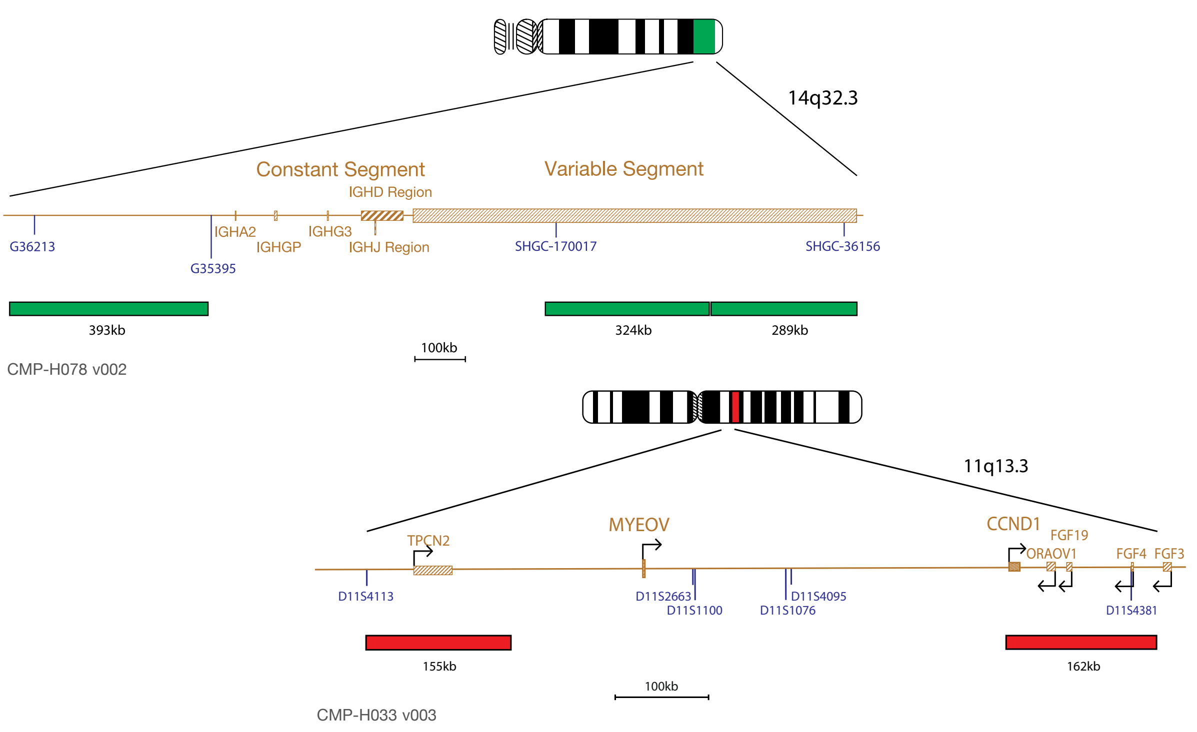

IVD: *In Vitro* Diagnostic Medical Device

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Cytocell aquarius

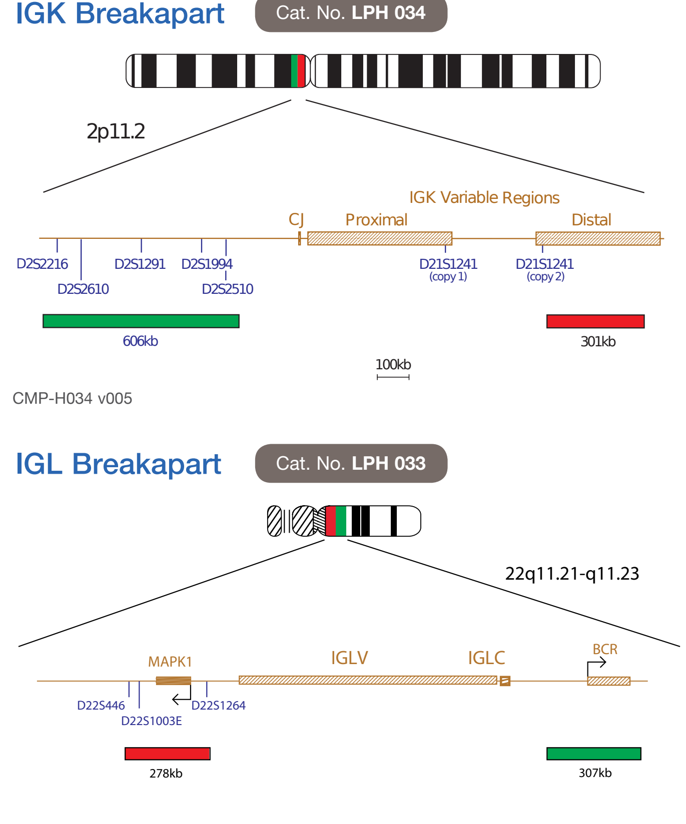
Cat. No. **LPH 034-S** (5 tests) Cat. No. **LPH 033-S** (5 tests)
Cat. No. **LPH 034** (10 tests) Cat. No. **LPH 033** (10 tests)

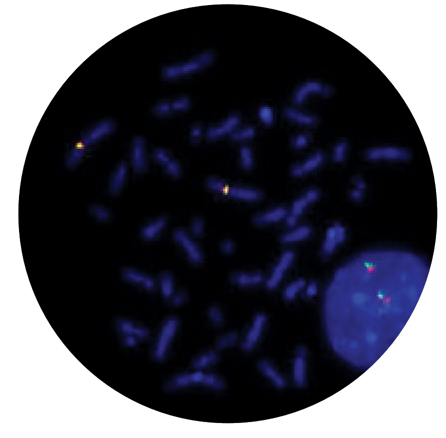
IGK Breakapart and IGL Breakapart*

Recurrent rearrangements involving the IGK (*immunoglobulin kappa locus*) gene at 2p11.2 or the IGL (*immunoglobulin lambda locus*) gene at 22q11, with a wide range of partner genes, are seen in lymphomas and haematological malignancies.

A large number of B-cell malignancies harbour translocations involving the immunoglobulin (IG) loci. The majority of cases will show rearrangements involving the IGH gene; however, variant translocations have been described in 5-10% of B-cell neoplasms which involve either the immunoglobulin kappa (IGK) light chain locus at 2p11.2 or the immunoglobulin lambda (IGL) light chain locus at 22q11[1,2].

Variant translocations involving the IG light chain loci are seen in Burkitt lymphoma and multiple myeloma, with the presence of a t(2;8)(p12;q24) MYC-IGK, or t(8;22)(q24;q11) MYC-IGL[3,5]. In diffuse large B-cell lymphoma (DLBCL), translocations may involve the BCL6 gene via t(2;3)(p12;q27) or t(3;22)(q27;q11) translocations, or the BCL2 gene via t(2;18)(p12;q21) or t(18;22)(q21;q11) translocations[6].





IGK Breakapart

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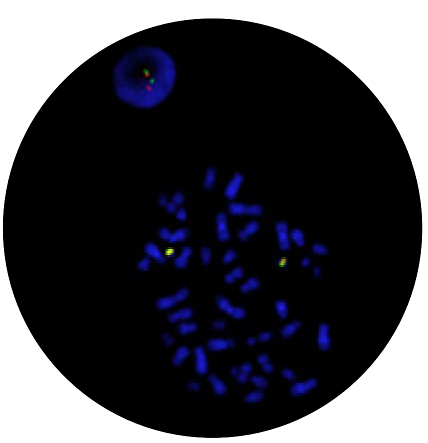

IGL Breakapart

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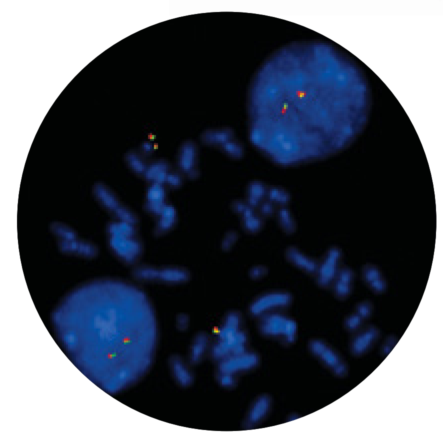
***Similar products are also available within the Haematopathology range, refer to page 85.**

IVD: *In Vitro* Diagnostic Medical Device

** These roundels are only intended to provide information supported by the literature and are not a reflection of the intended purpose of this product.

MLL (KMT2A) Breakapart



The KMT2A *(lysine methyltransferase 2A)* gene at 11q23.3 is commonly rearranged in acute leukaemias, especially in infant leukaemia and in secondary leukaemia, following treatment with DNA topoisomerase II inhibitors[1].

The KMT2A gene has a great homology with the drosophila trithorax gene and encodes for a histone methyltransferase, which functions as an epigenetic regulator of transcription. KMT2A translocations result in the production of a chimeric protein in which the amino-terminal portion of KMT2A is fused to the carboxy-terminal portion of the fusion partner gene. The functional protein plays a critical role in embryonic development and haematopoiesis[1,2,3,4].

KMT2A rearrangements can be detected in approximately 80% of infants with acute lymphoblastic leukaemia (ALL) and in 5-10% of paediatric and adult ALLs[3,4]. They can also be found in 60% of infant acute myeloid leukaemia (AML) and in 3% of *de novo* and 10% of therapy related adult AML cases[3,5]. To date, more than 70 partners have been identified with the most common translocations being MLL-AFF1; t(4;11)(q21;q23.3), MLL-MLLT4; t(6;11)(q27;q23.3), MLL-MLLT3; t(9;11)(p22;q23.3) and MLL-MLLT1; t(11;19)(q23.3;p13.3)[1].

Historically, KMT2A rearrangements in acute leukaemia were associated with a poorer outcome, but recent studies have shown that the prognosis is highly dependent on the fusion partner and it may differ between children and adults[1].

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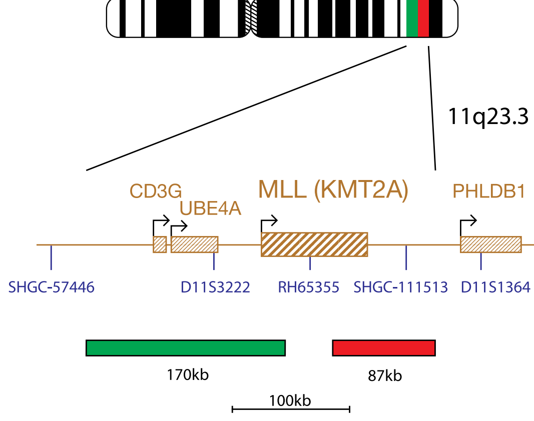

CMP-H036 v006

IVD: *In Vitro* Diagnostic Medical Device
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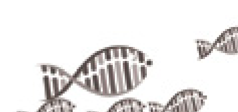
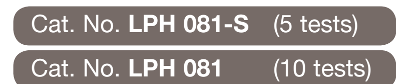
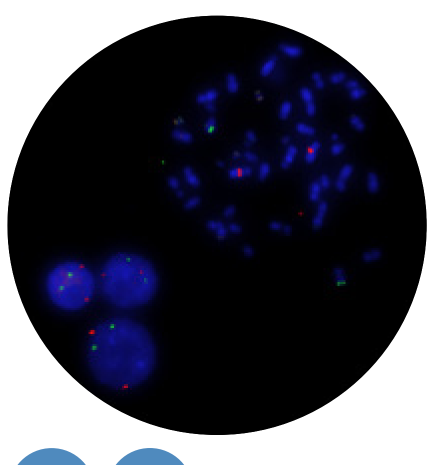




MLL (KMT2A)/AFF1 Translocation, Dual Fusion

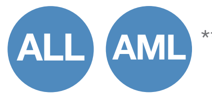


The KMT2A (*lysine methyltransferase 2A*) gene located at 11q23.3 and AFF1 (*AF4/FMR2 family member 1*) gene at 4q21.3 are involved in translocation t(4;11)(q21;q23.3), the most frequently observed translocation involving the KMT2A gene, in acute lymphoblastic leukaemia (ALL)[1].

The t(4:11)(q21;q23.3) translocation results in the generation of two reciprocal fusion genes: KMT2A-AFF1 and AFF1-KMT2A – the leukaemic properties of the first have been documented but the role of the AFF1-KMT2A fusion protein is still under debate[2,3,4].

UK best practice guidelines suggest that, if chromosome analysis is unsuccessful but FISH indicates a rearrangement of KMT2A, then further attempts to identify the t(4;11) must be made as the t(4;11)(q21;q23) is associated with a poor prognosis, and patients with this translocation may be treated on the high risk arm of MRC protocols[5].

The MLL/AFF1 translocation, dual fusion probe allows both fusion genes, generated by the t(4;11)(q21;q23) translocation, to be detected.



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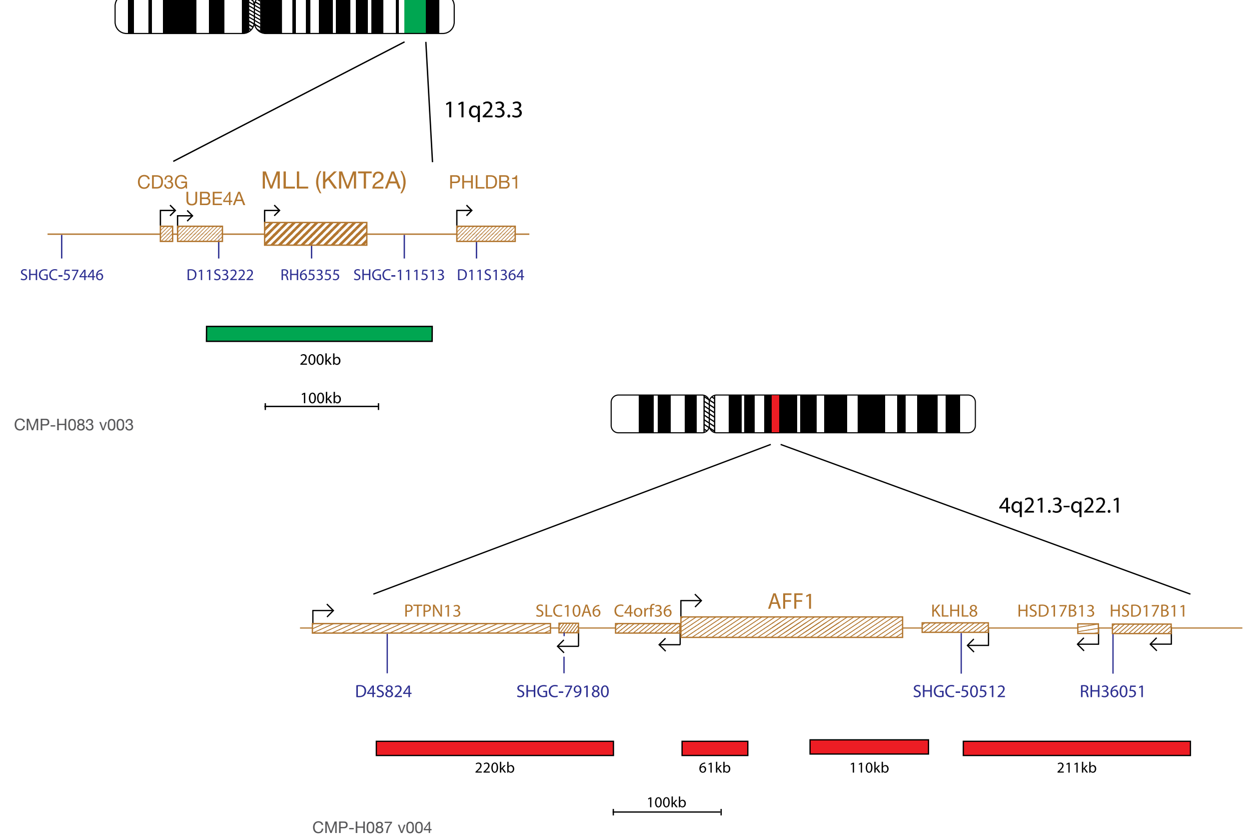

IVD: *In Vitro* Diagnostic Medical Device

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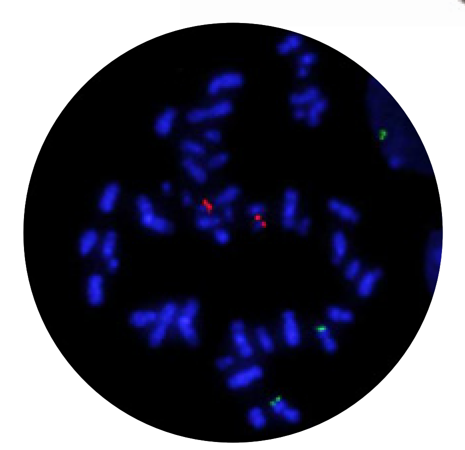
MLL (KMT2A)/MLLT1†, MLL (KMT2A)/MLLT3† and MLL (KMT2A)/MLLT4 (AFDN)† Translocation, Dual Fusion

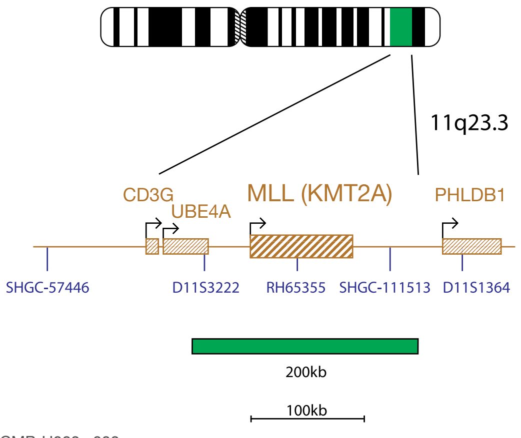


For research use only **RUO**

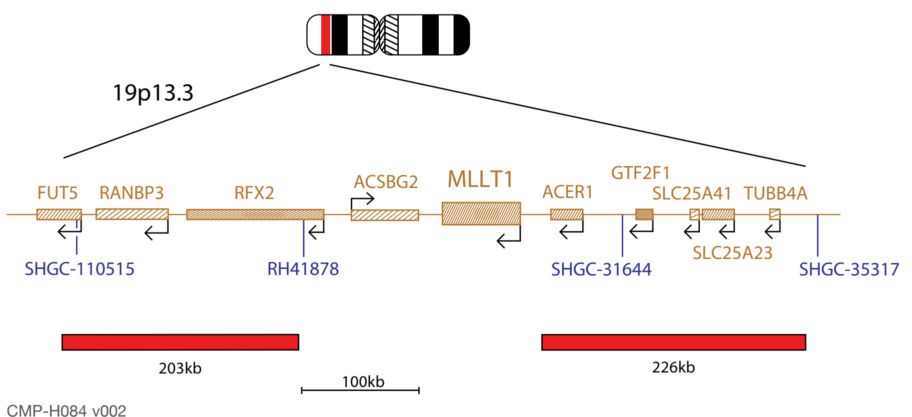
The MLL probe, labelled in green, covers a 200kb region including the MLL (KMT2A) gene. The MLLT1 probe, labelled in red, consists of two clones (203kb and 226kb) that flank the MLLT1 gene.

MLL (KMT2A)/MLLT1

Cat. No. **RU-LPH 082†**



CMP-H083 v003



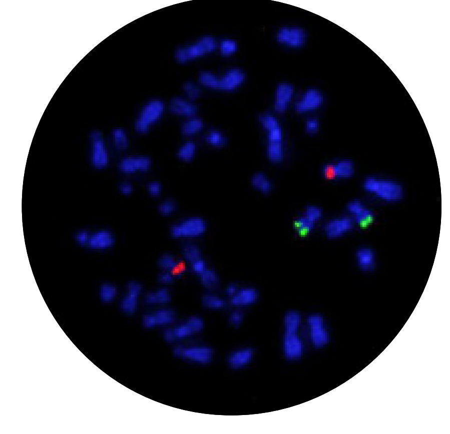
CMP-H084 v002

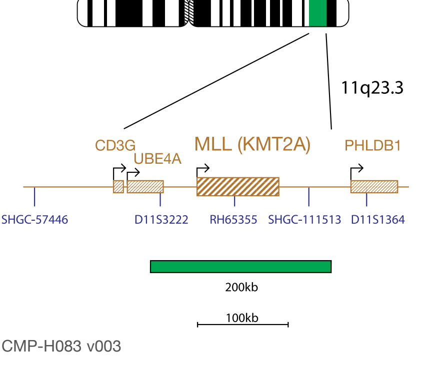
† RUO: For research use only, not for use in diagnostic procedures.

MLL (KMT2A)/MLLT3

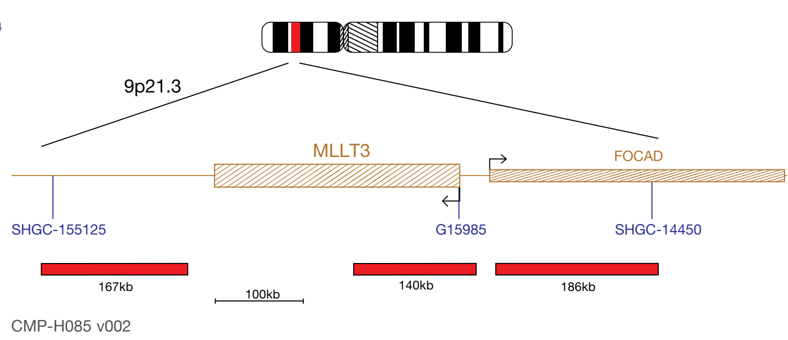
Cat. No. **RU-LPH 083†**

The MLL probe, labelled in green, covers a 200kb region including the MLL (KMT2A) gene. The MLLT3 probe, labelled in red, consists of a 140kb clone that covers the 5' end of the MLLT3 gene and two clones (167kb and 186kb) that flank this.





CMP-H083 v003

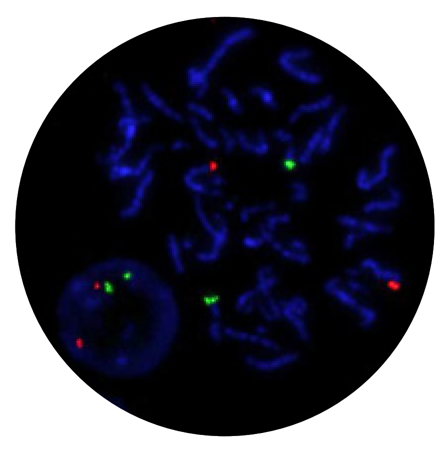


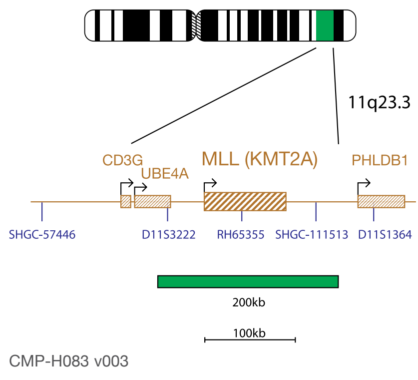
CMP-H085 v002

MLL (KMT2A)/MLLT4 (AFDN)

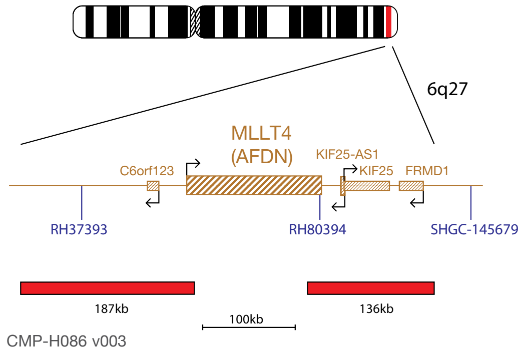
Cat. No. **RU-LPH 084†**

The MLL probe, labelled in green, covers a 200kb region including the MLL (KMT2A) gene. The MLLT4 probe, labelled in red, consists of two clones (187kb and 136kb) that flank the MLLT4 (AFDN) gene.





CMP-H083 v003



CMP-H086 v003

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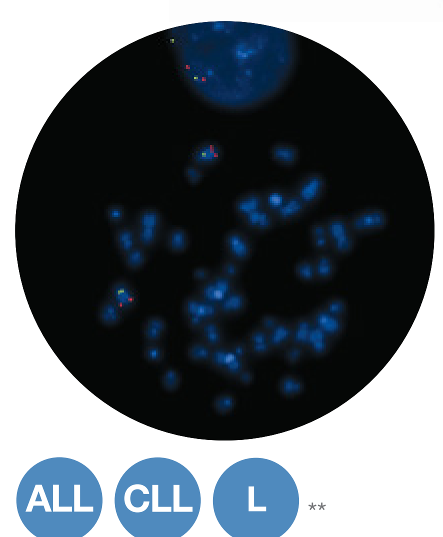
MYB Deletion



ALL **CLL** **L** **

MYB (*MYB proto-oncogene, transcription factor*) at 6q23.3 is a transcription factor essential for haematopoiesis[1].

The long arm of chromosome 6 (6q) is frequently involved in chromosomal abnormalities in human cancer, including haematological malignancies[1]. Deletions of chromosome 6q are found in acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL) and high grade nodal and extranodal B-cell lymphoma, but also in breast carcinoma, melanoma, ovarian carcinoma and renal cell carcinoma[2,3].

Additionally, rearrangements involving MYB have been reported in T-ALL, for example the t(6;7)(q23;q34) translocation involving TRB seen in approximately 6% of patients, and focal duplications of the MYB locus, which are present in about 10% of patients[1,4].

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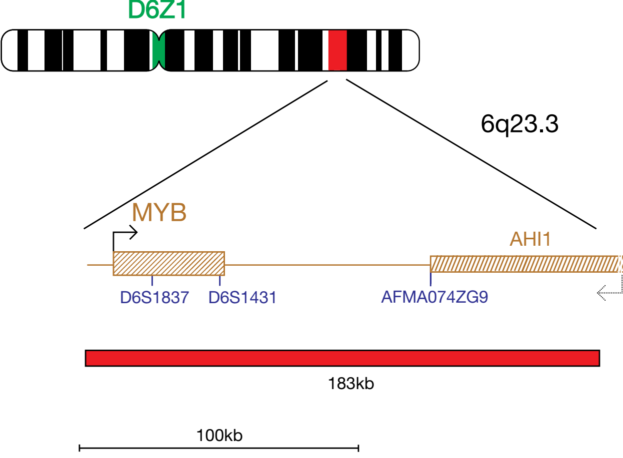

CMP-H037 v002

IVD: *In Vitro* Diagnostic Medical Device

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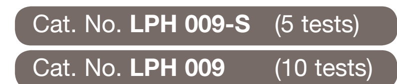
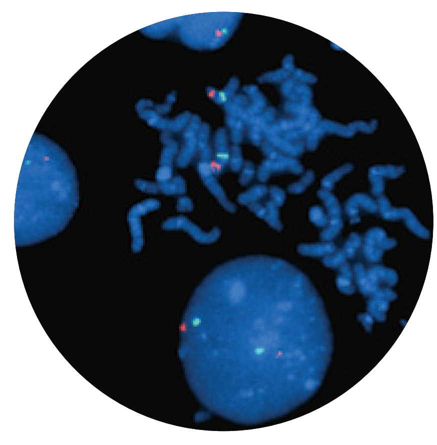
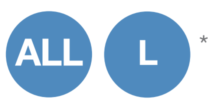


P16 (CDKN2A) Deletion*





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The CDKN2A (*cyclin-dependent kinase inhibitor 2A*) gene at 9p21 is a tumour suppressor gene that has been shown to be deleted in wide range of human malignancies.

Loss of the CDKN2A gene results in cellular proliferation and dysregulation of pro-apoptotic pathways. There are two proteins produced by the CDKN2A gene: $p16^{INK4a}$ and $p14^{ARF}$, these protein products have been linked to two tumour suppressor pathways: the RB pathway and the p53 pathway, respectively[1].

Deletions of 9p that include the CDKN2A gene are frequently reported in patients with acute lymphoblastic leukaemia (ALL): in approximately 30% of adult B-cell ALLs, 30% of childhood ALLs and up to 50% of T- cell ALLs. In adult B-cell ALL, CDKN2A deletions are frequently acquired in disease progression[2,3,4,5].

Deletions including the CDKN2A locus have been reported in up to a third of patients with diffuse large B-cell lymphoma (DLBCL)[6] and, in glioma, CDKN2A loss has been implicated with shorter overall survival in WHO grade I-III astrocytomas[7].

Losses of the CDKN2A region have also been reported in malignant mesothelioma, melanoma, and bladder cancer[8,9,10].

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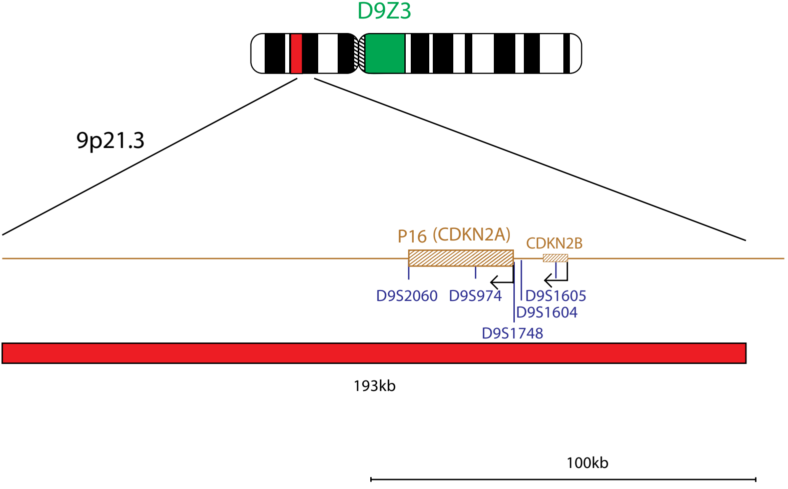

CMP-H038 v002

***A similar product is also available within the Haematopathology range, refer to page 88.**

IVD: *In Vitro* Diagnostic Medical Device

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Cytocell aquarius

Cat. No. **LPH 017-S** (5 tests)
Cat. No. **LPH 017** (10 tests)

P53 (TP53) Deletion*

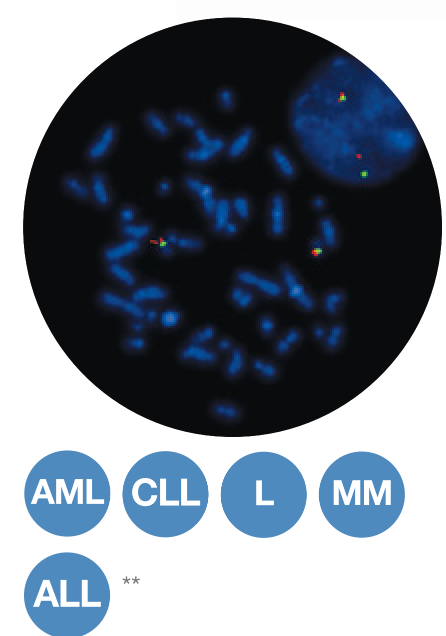
The TP53 (*tumor protein p53*) gene at 17p13 is a tumour-suppressor gene that has been shown to be deleted in a wide range of human malignancies.

The TP53 gene is one of the most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Screening for TP53 loss is important as deletions or losses of the short arm of chromosome 17, which includes the TP53 region, are reported in many cancers and are often associated with disease progression, inferior response to treatment and/or a poor prognosis.

In particular, loss of TP53 is reported in 10% of patients with chronic lymphocytic leukaemia (CLL), and is considered to be the poorest prognostic marker in that disease[1,2]. In acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), TP53 loss is associated with a poor outcome and is often seen as a marker of disease progression or secondary disease[3-5].

TP53 loss in patients with multiple myeloma is a late event, where is seen as a marker of disease progression and is associated with a very poor prognosis[6,7].

In non-Hodgkin lymphoma, TP53 losses are reported in diffuse large B-cell lymphoma (DLBCL) often as part of 'dual-hit' lymphoma or plasmablastic phenotypes[8]. In mantle cell lymphoma (MCL), TP53 losses are associated with a poor outcome, and with a dismal outcome when seen with concurrent CDKN2A deletions[9].



AML CLL L MM ALL **

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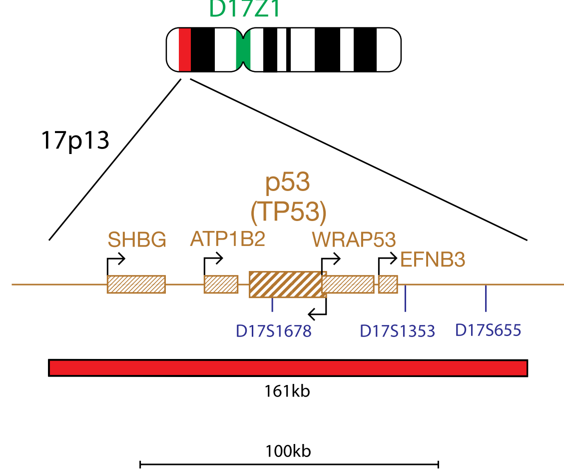

CMP-H039 v006

***A similar product is also available within the Haematopathology range, refer to page 89.**

IVD: *In Vitro* Diagnostic Medical Device

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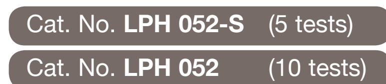
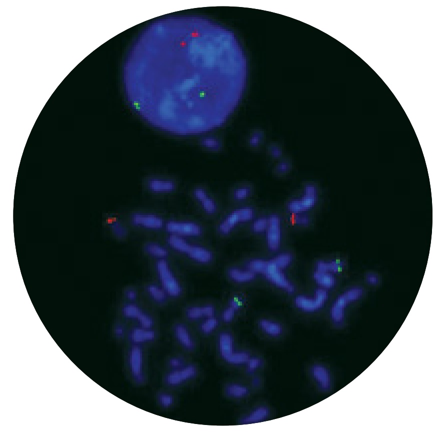


P53 (TP53)/ATM Probe Combination



The tumour suppressor TP53 (*tumor protein p53*) gene at 17p13 and the protein kinase ATM (*ATM serine/threonine kinase*) gene at 11q22.3, are frequently deleted in cases of chronic lymphocytic leukaemia (CLL).

CLL is the most common leukaemia in adults; its course can vary from very indolent to rapidly progressive. Due to the low mitotic activity of the leukaemic cells *in vitro*, clonal chromosomal abnormalities are detected in 40-50%[2] of cases by conventional cytogenetics using B-cell mitogens, whereas FISH analysis identifies chromosomal aberrations in approximately 80% of CLLs[2]. Screening for deletions of ATM and/or TP53 is vital to allow informed therapy choices for CLL patients, as deletions of TP53 and ATM confer poorer prognosis in this disease[1,2,3].

The TP53 gene is one of most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Loss of TP53 is reported in 10% of patients with CLL, and is considered to be the poorest prognostic marker in that disease[1,4].

ATM is an important checkpoint gene involved in the management of cell damage; its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway[5]. Loss of ATM is reported in 18% of patients with CLL, and is considered a poor prognostic marker in that disease[2].

Analysis of the ATM/TP53 interaction in CLL has shown that TP53 and ATM play an important role in the proliferation of lymphoid cancer[5], It has been shown that ATM enhances the phosphorylation of TP53, should the damage be so great that the cell requires destruction by apoptosis (which is mediated by TP53). Deletion of ATM removes this checkpoint activity and hence activation of TP53. Thus, there is no attempt made to repair, or apoptosis of, damaged cells, despite the presence of TP53. In the absence of ATM, damaged cells are allowed to continue to proliferate[6].

**

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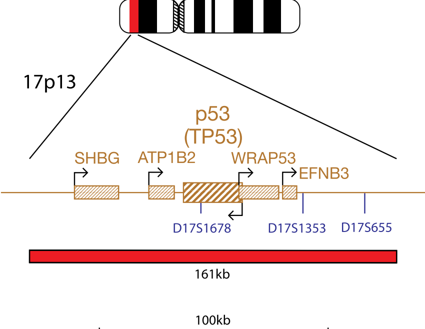

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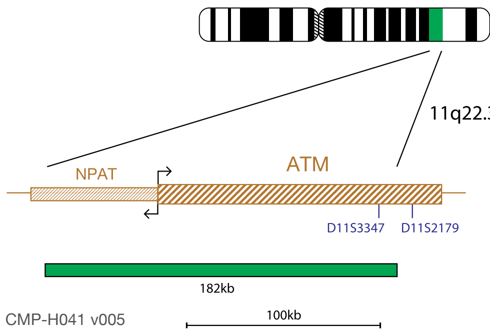

CMP-H041 v005

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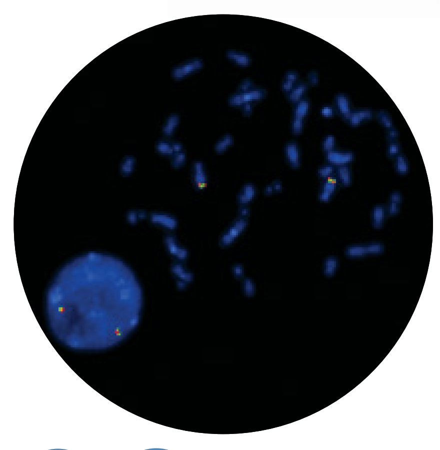
PDGFRB Breakapart



Rearrangements involving the PDGFRB (*platelet derived growth factor receptor beta*) gene at 5q32 are reported in both myeloid and lymphoid neoplasms.

In the 2008 World Health Organisation (WHO) classification of myeloid neoplasms and acute leukaemia, a new subgroup of myeloid neoplasms was introduced: *Myeloid and Lymphoid Neoplasms with Eosinophilia and Abnormalities of PDGFRA, PDGFRB or FGFR1*. These neoplasms constitute three specific disease groups, with some shared features[1].

The myeloid neoplasms with PDGFRB rearrangements are characterised by constitutive activation of the PDGFRB gene product[1]. The activation is most commonly caused by a t(5;12)(q31-q33;p13) translocation which results in an ETV6-PDGFRB fusion gene. Patients with this fusion have been shown to be responsive to tyrosine kinase inhibitors (TKIs)[2], which specifically inhibits the kinase activity of PDGFRB.

In B-ALL, gene expression profiling has identified an unusual genetic subgroup, the BCR-ABL1-like or Philadelphia chromosome-like (Ph-like) ALL, which represents about 15% of paediatric ALL cases and has an unfavourable outcome[3,4]. Patients with this expression signature are characterised by genetic alterations, such as rearrangements, mutations and deletions of a range of kinase and cytokine receptors, including PDGFRB rearrangements. Known PDGFRB partners are EBF1 at 5q33, SSBP2 at 5q14, TNIP1 at 5q33 and ZEB2 at 2q22. It is crucial to detect such rearrangements, as patients could benefit from treatment with tyrosine kinse inhibitors (TKIs)[3,4,5].

MPN **

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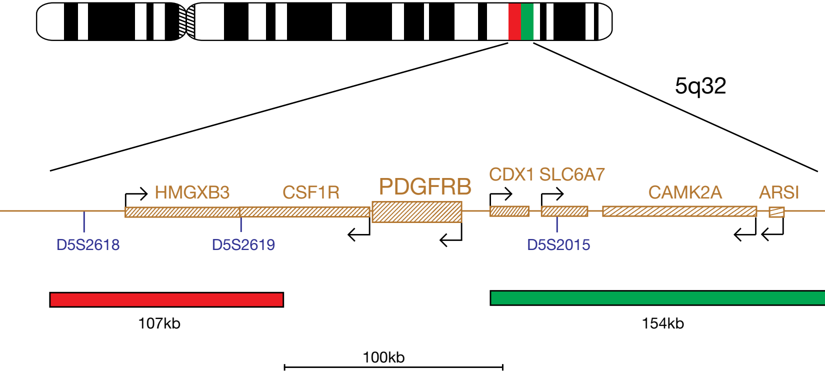

CMP-H042 v003

IVD: *In Vitro* Diagnostic Medical Device
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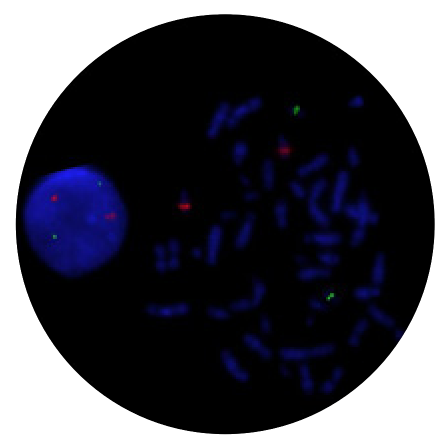

FAST PML/RARα (RARA) Translocation, Dual Fusion

The PML (*promyelocytic leukemia*) gene is located at 15q24.1 and the RARA (*retinoic acid receptor alpha*) gene is located at 17q21.2. The translocation t(15;17)(q24;q21) gives rise to the PML-RARA fusion gene and is the diagnostic hallmark of acute promyelocytic leukaemia (APL). This FAST PML/RARα FISH probe allows rapid detection of the rearrangement, with only one hour of hybridisation required.

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The PML-RARA fusion gene is created by the t(15;17)(q24;q21) translocation, found in more than 90% of cases of APL, a leukaemia that comprises 5-8% of cases of acute myeloid leukaemia (AML)[1,2]. In a subset of cases, variant RARA translocations can be observed. Known fusion partners include NPM1 at 5q35, NUMA1 at 11q13, ZBTB16 (PLZF) at 11q23, STAT5B at 17q21, PRKAR1A at 17q24, FIP1L1 at 4q12 and BCOR at Xp11[3,4,5].

PML and RARA have both been implicated in normal haematopoiesis. PML possesses growth suppressor and proapoptotic activity whereas RARA is a transcription factor that mediates the effect of retinoic acid at specific response elements[6]. PML-RARA fusion protein behaves as an altered retinoic acid receptor with an ability of transmitting oncogenic signalling[7].

Immediate treatment of APL patients is critical, due to fatal coagulation disorders and life-threatening haemorrhage in diagnosis. Prior to the introduction of all-trans-retinoic-acid (ATRA) and arsenic trioxide (ATO) in APL treatment protocols, the disease had a poor prognosis; however, since the introduction of these therapies, the overall survival rate has improved dramatically, with nearly 90%[5] of patients cured. Patients with variant RARA translocations show variable sensitivity to treatment, with some patients showing resistance to treatment protocols[3,5]. It is therefore important to differentiate between APL patients with PML-RARA fusion and those patients with variant RARA translocations.

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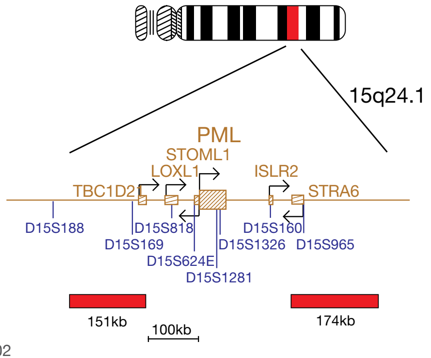
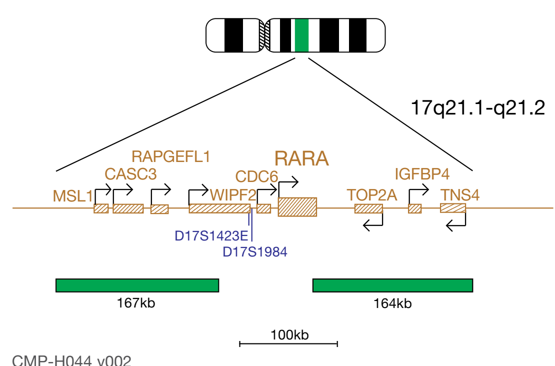


CMP-H043 v002



CMP-H044 v002

IVD: *In Vitro* Diagnostic Medical Device
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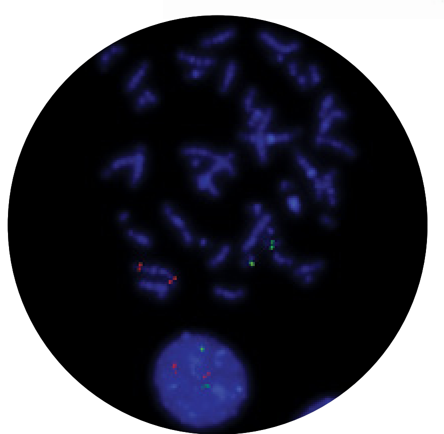
Cat. No. **LPH 023-S** (5 tests)
Cat. No. **LPH 023** (10 tests)

PML/RARα (RARA) Translocation, Dual Fusion



The PML (*promyelocytic leukemia*) gene is located at 15q24.1 and the RARA (*retinoic acid receptor alpha*) gene is located at 17q21.2. The translocation t(15;17)(q24;q21) gives rise to the PML-RARA fusion gene and is the diagnostic hallmark of acute promyelocytic leukaemia (APL).

The PML-RARA fusion gene is created by the t(15;17)(q24;q21) translocation, found in more than 90% of cases of APL, a leukaemia that comprises 5-8% of cases of acute myeloid leukaemia (AML)[1,2]. In a subset of cases, variant RARA translocations can be observed. Known fusion partners include NPM1 at 5q35, NUMA1 at 11q13, ZBTB16 (PLZF) at 11q23, STAT5B at 17q21, PRKARIA at 17q24, FIP1L1 at 4q12 and BCOR at Xp11[3,4,5].

PML and RARA have both been implicated in normal haematopoiesis. PML possesses growth suppressor and proapoptotic activity whereas RARA is a transcription factor that mediates the effect of retinoic acid at specific response elements[6]. PML-RARA fusion protein behaves as an altered retinoic acid receptor with an ability of transmitting oncogenic signalling[7].

Immediate treatment of APL patients is critical, due to fatal coagulation disorders and life-threatening haemorrhage in diagnosis. Prior to the introduction of all-trans-retinoic-acid (ATRA) and arsenic trioxide (ATO) in APL treatment protocols, the disease had a poor prognosis; however, since the introduction of these therapies, the overall survival rate has improved dramatically, with nearly 90%[5] of patients cured. Patients with variant RARA translocations show variable sensitivity to treatment, with some patients showing resistance to treatment protocols[3,5]. It is therefore important to differentiate between APL patients with PML-RARA fusion and those patients with variant RARA translocations.

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4. Zhang *et al*., Blood Reviews 2015;29(2):101-125
5. Tomita *et al*., International Journal of Haematology 2013;97(6):717-725
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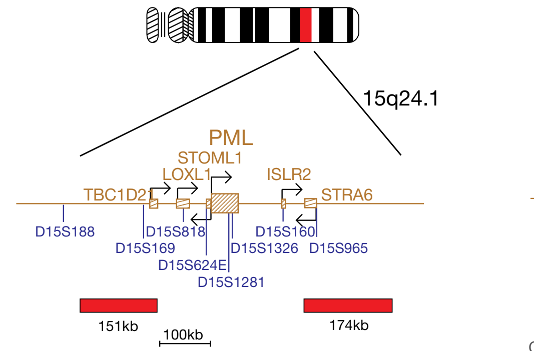

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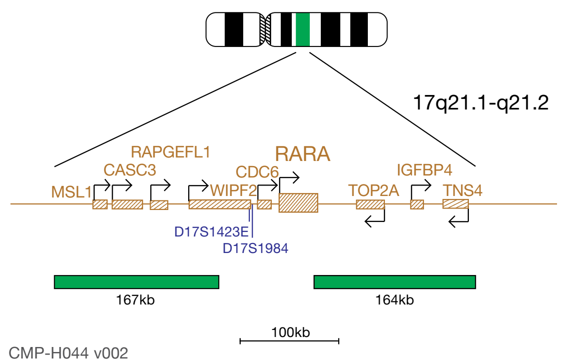

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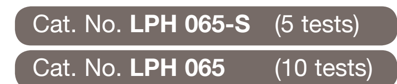


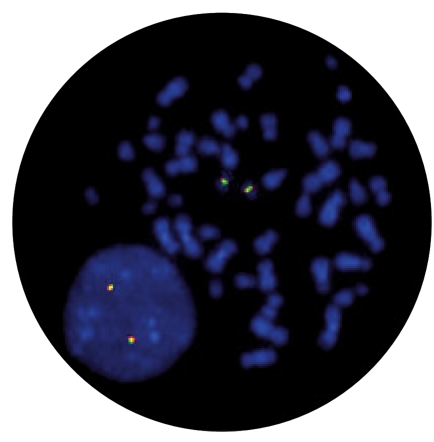
RARα (RARA) Breakapart

The PML (*promyelocytic leukemia*) gene is located at 15q24.1 and the RARA (*retinoic acid receptor alpha*) gene is located at 17q21.2. In the vast majority of acute promyelocytic leukaemia (APL) cases, the RARA gene at 17q21.2 fuses with PML gene at 15q24.1; however, in <5% of cases of APL, RARA is fused to alternative partner[1].

Known variant fusion partners include NPM1 at 5q35, NUMA1 at 11q13, ZBTB16 (PLZF) at 11q23, STAT5B at 17q21, PRKARIA at 17q24, FIP1L1 at 4q12 and BCOR at Xp11[1,2,3].

Patients with variant RARA translocations may show variable sensitivity to treatment with some patients showing resistance to treatment protocols[1,3]. It is therefore important to differentiate between APL patients with PML-RARA fusion and those patients with variant RARA translocations.

This breakapart probe will detect rearrangements of the RARA gene, irrespective of partner genes or chromosomes involved.



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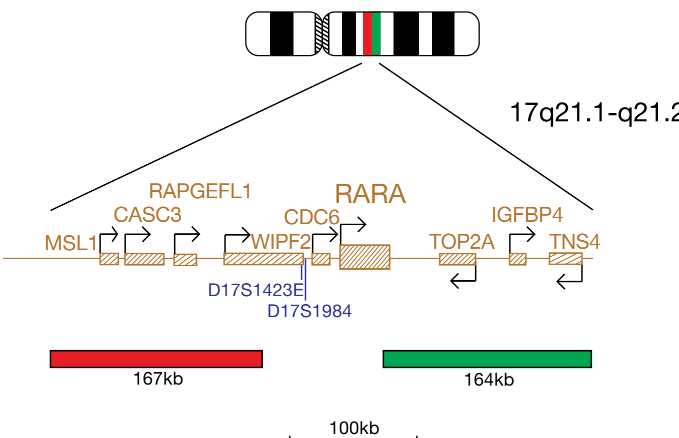

CMP-H076 v001

IVD: *In Vitro* Diagnostic Medical Device

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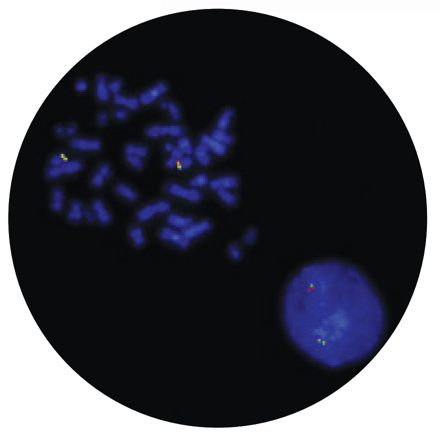
TCL1 Breakapart

The TCL1A (*T-cell leukemia/lymphoma 1A*) and TCL1B (*T-cell leukemia/lymphoma 1B*) genes at 14q32 have been shown to be dysregulated through close juxtaposition of enhancer elements of the T-cell receptor (TCR) genes[1].

Dysregulation of gene transcription is a feature of all acute leukaemias. In T-cell neoplasms, this is brought about by altered expression of normal transcription factor proteins, often as a consequence of chromosomal rearrangements placing these genes into close proximity of the promoter and enhancer elements of the TCR genes: TRA and TRD at 14q11.2, TRB at 7q34 and TRG at 7p14[2,3].

In T-cell prolymphocytic leukaemia (T-PLL) the T-cell Leukaemia 1A/1B gene cluster on chromosome 14q32 has been shown to be involved in a number of different chromosomal rearrangements, including the t(14;14)(q11;q32) and inv(14)(q11;q32), which bring elements of the cluster into close juxtaposition to, and under the control of, the TCR gene promoters and enhancers. There are two breakpoint regions in the gene cluster, each of which are observed in different neoplasms, though both are involved in either the inv(14) or t(14;14). Breakpoints are concentrated in regions centromeric and telomeric to the TCL1A, TCL6 and TCL1B genes[4].



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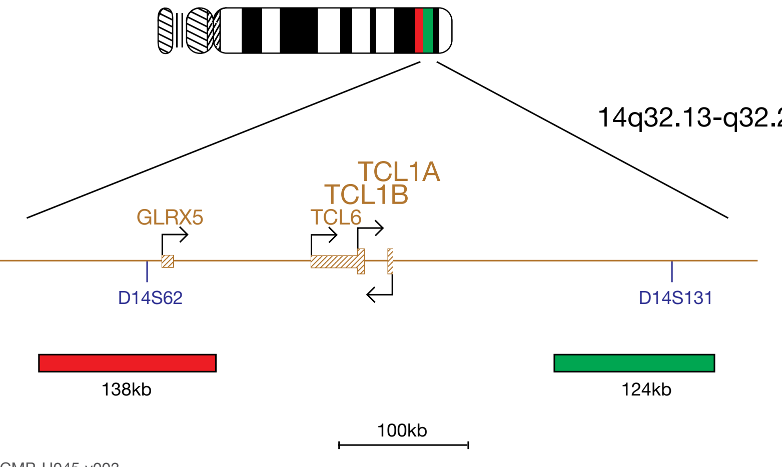

CMP-H045 v003

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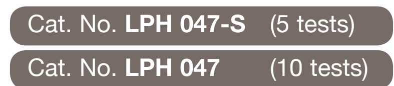
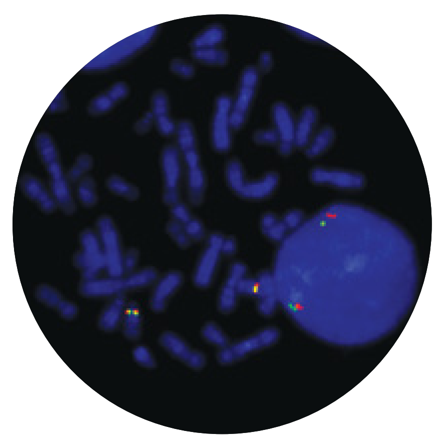


TCRAD Breakapart



Chromosomal translocations with breakpoints in alpha and delta T-cell receptor (TCR) gene loci at 14q11.2 are recurrent in several T-cell malignancies including T-cell acute lymphoblastic leukaemia (T-ALL)[1].

T-cell acute lymphoblastic leukaemia (T-ALL) is an aggressive malignancy of the lymphoblasts committed to the T-cell lineage and represents 15% of childhood and 25% of adult ALL[2,3]. Karyotyping reveals recurrent translocations that activate a small number of oncogenes in 25-50% of T-ALLs but, with FISH, further cryptic abnormalities can be revealed[2].

The most common chromosomal rearrangements, found in approximately 35%[2] of T-ALLs, involve the alpha and delta T-cell receptor loci (TRA and TRD) at 14q11.2, the beta TCR locus (TRB) at 7q34 and the gamma TCR (TRG) at 7p14. In most cases the juxtaposition of oncogenes next to the TCR regulatory sequences leads to the deregulated expression of these genes[2,4,5].

The TRA/D complex at 14q11.2 has been shown to be involved in a number of different translocations in T-ALL. These include the t(10;14)(q24;q11) involving TLX1; the t(1;14)(p32;q11) involving TAL1; the t(14;21)(q11;q22) involving the OLIG2; the t(11;14)(p15;q11) involving LMO1 and the t(11;14)(p13;q11) involving LMO2[2].

In addition to T-ALL, TRA/D translocations are recurrent in T-non-Hodgkin's lymphoma and T-prolymphocytic leukaemia. They have also been reported in cases of ataxia telangiectasia (AT)[1].

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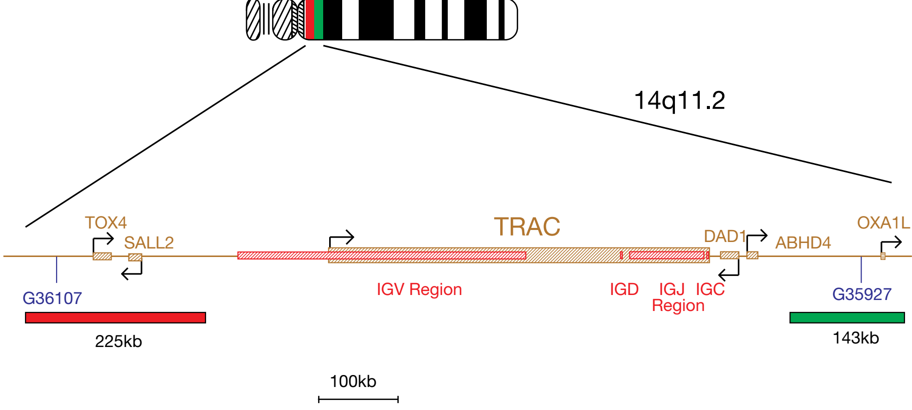

CMP-H046 v002

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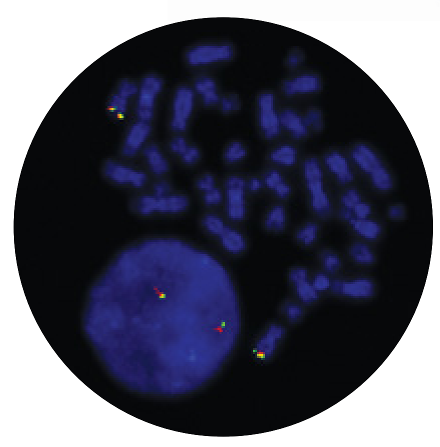
Cat. No. **LPH 048** (10 tests)



TCRB (TRB) Breakapart

Chromosomal translocations with breakpoints in beta T-cell receptor (TCR) gene loci at 7q34 are recurrent in several T-cell malignancies including T-cell acute lymphoblastic leukaemia (T-ALL)[1].

T-cell acute lymphoblastic leukaemia (T-ALL) is an aggressive malignancy of the lymphoblasts committed to the T-cell lineage and represents 15% of childhood and 25% of adult ALL[2,3]. Karyotyping reveals recurrent translocations that activate a small number of oncogenes in 25-50% of T-ALLs but with FISH further cryptic abnormalities can be revealed[2].

The most common chromosomal rearrangements, found in approximately 35%[2] of T-ALLs, involve the alpha and delta T-cell receptor loci (TRA and TRD) at 14q11.2, the beta TCR locus (TRB) at 7q34 and the gamma TCR (TRG) at 7p14. In most cases the juxtaposition of oncogenes next to the TCR regulatory sequences leads to the deregulated expression of these genes[2,4,5].

TRB at 7q34 is rearranged with the genes TLX1 at 10q24, HOX cluster at 7p15, LYL1 at 19p13, TAL2 at 9q32, LCK at 1p34 and NOTCH1 at 9q34 via the t(7;10)(q34;q24); t(7;7)(p15;q34); t(7;19)(q34;p13); t(7;9)(q34;q32); t(1;7)(p34;q34) and t(7;9)(q34;q34) translocations respectively[2].

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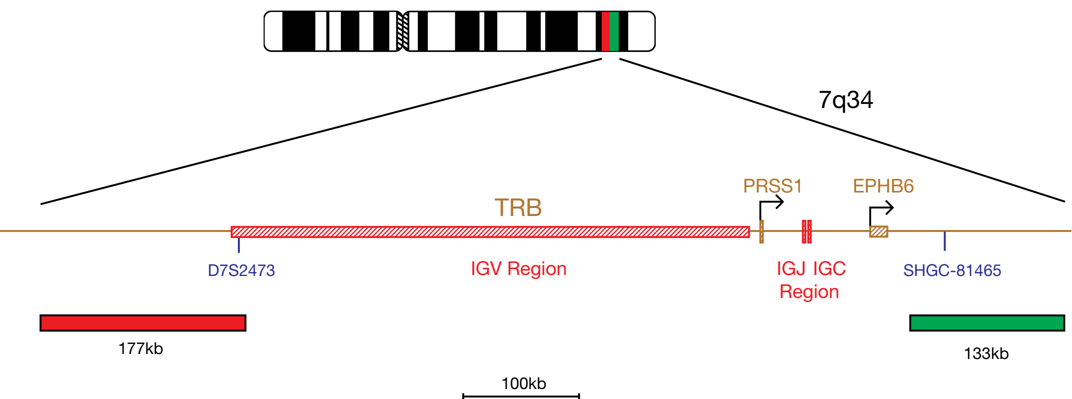
2. Graux *et al*., Leukemia 2006;20:1496-1510
3. Cauwelier *et al*., Leukemia 2007;21:121-128
4. Swerdlow *et al*.,editors, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, France, 4th edition, IARC, 2017
5. Gesk *et al*., Leukemia 2003;17:738-745



CMP-H047 v002

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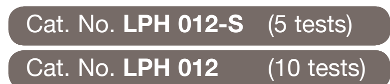
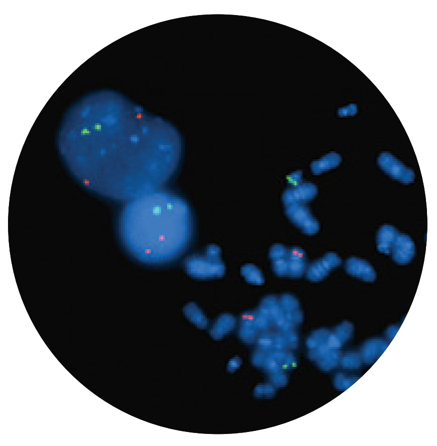


TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion



The cytogenetically-cryptic t(12;21)(p13;q22) translocation between ETV6 (*ets variant 6*) at 12p13 and RUNX1 (*RUNX family transcription factor 1*) at 21q22, results in the ETV6-RUNX1 chimeric fusion gene[1].

The ETV6 and RUNX1 genes both encode transcription factors; ETV6 has been shown to be required for proper transcription during haematopoiesis within the bone marrow [1,2]. The ETV6-RUNX1 protein converts RUNX1 to a transcriptional repressor and causes overexpression of the erythropoietin receptor (EPOR) and activation of downstream JAK-STAT signaling[1].

B-lymphoblastic leukaemia/lymphomas with t(12;21)(p13;q22) translocations form a recognised disease entity according to the World Health Organisation (WHO) classification of myeloid neoplasms and acute leukaemia. This is the most common sub-group of childhood B-ALL accounting for about 25% of cases[3]. As the t(12;21)(p13;q22) translocation is cytogenetically-cryptic, FISH is an important diagnostic tool for this leukaemia[4].

B-ALL with ETV6-RUNX1 is considered to have a favourable outcome with cure rates more than 90%[3]. Late relapses have been reported; these have been attributed to the presence of persistent preleukaemic clones that survived chemotherapy[3,5].

ETV6 has also been shown to be deleted in some children with ALL, with loss of heterozygosity (LOH) of chromosome 12p12-13; these deletions are often seen in the presence of ETV6-RUNX1 translocations[6].

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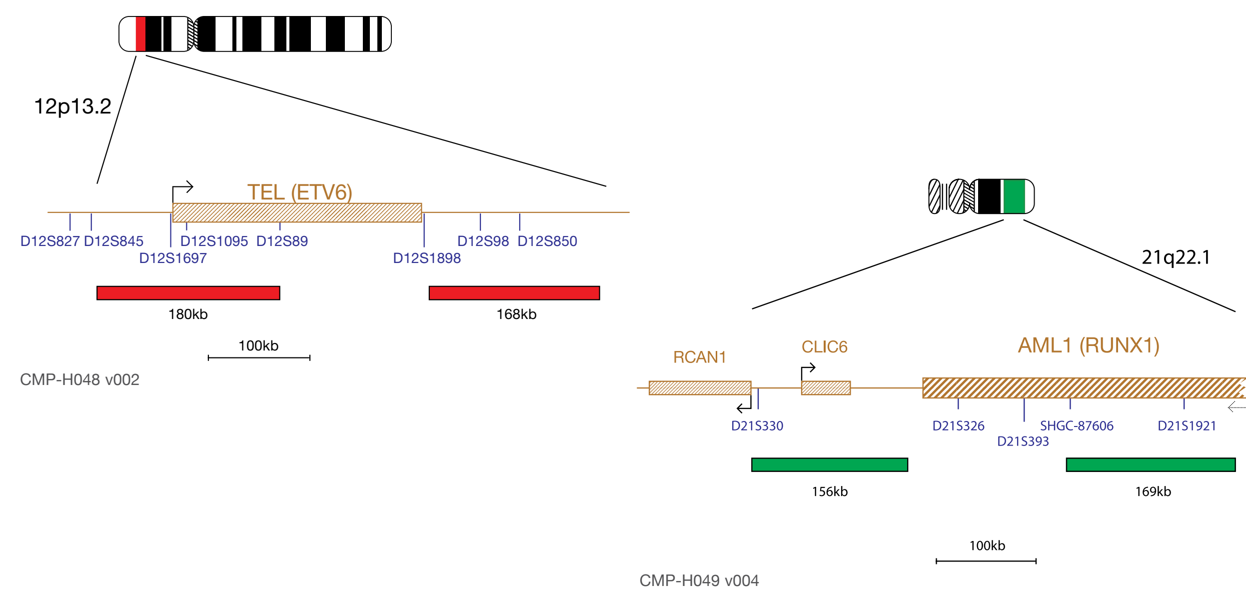


IVD: *In Vitro* Diagnostic Medical Device

** These roundels are only intended to provide information supported by the literature and are not a reflection of the intended purpose of this product.

Cat. No. **LPH 049-S** (5 tests)
Cat. No. **LPH 049** (10 tests)

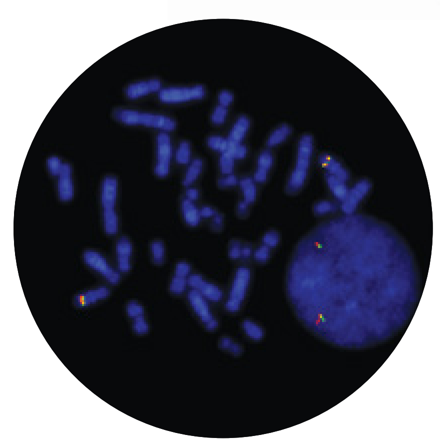
Haematology

TLX1 Breakapart

The TLX1 (*T-cell leukemia homeobox 1*) gene at 10q24 is aberrantly expressed in 30% of adult and 5-10% of childhood T-cell acute lymphoblastic leukaemia (T-ALL)[1,2].

Dysregulation of gene transcription is a feature of all acute leukaemias. In T-cell neoplasms, this is brought about by altered expression of normal transcription factor proteins, often as a consequence of chromosomal rearrangements placing these genes into close proximity of the promoter and enhancer elements of the TCR genes: TRA and TRD at 14q11.2, TRB at 7q34 and TRG at 7p14[3,4].

Murine studies show that expression of mouse homologues of TLX1 can immortalise haematopoietic cells *in vitro* as the first of a potential two-hit mechanism leading to full malignancy[2]. This work suggests that TLX1 is an oncogene that can become dysregulated via the translocations t(10;14)(q24;q11) or t(7;10)(q35;q24), placing it into close proximity with TRA/D and TRB elements respectively[5]. Additionally, TLX1 is frequently activated in T-ALL in the absence of an overt genetic rearrangement. T-ALLs with TLX1 expression show a more favourable outcome than other T-ALLs[5].



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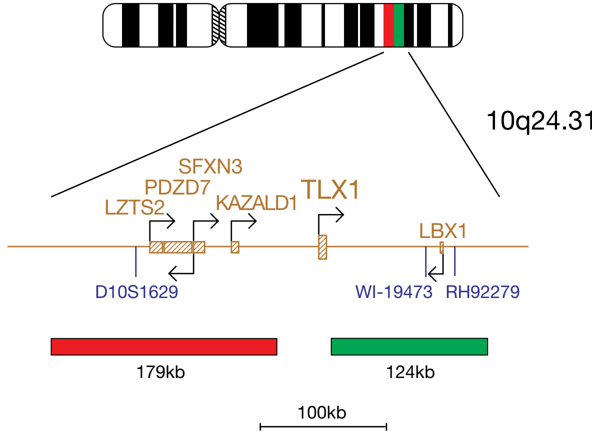

CMP-H050 v002

IVD: *In Vitro* Diagnostic Medical Device
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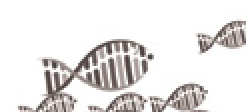
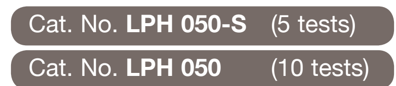
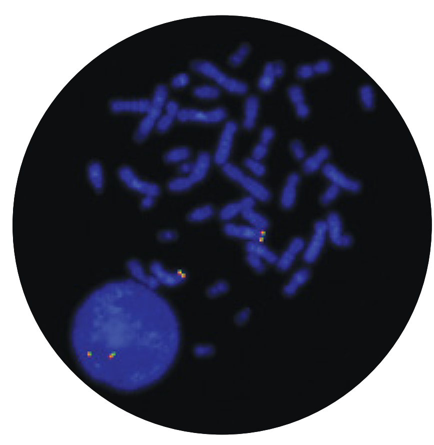




TLX3 Breakapart



The TLX3 (*T-cell leukemia homeobox 3*) gene at 5q35 can be aberrantly expressed in T-cell acute lymphoblastic leukaemia (T-ALL) due to a cryptic translocation[1].

Unlike TLX1, the dysregulation of TLX3 is not brought about by close juxtaposition with T-cell receptor genes, instead, it is brought into contact with another gene that is highly expressed in normal T-cell differentiation: BCL11B at 14q32[2]. The t(5;14)(q35;q32) translocation is cryptic and the breakpoint does not actually disrupt TLX3 but, in the majority of cases, occurs within or downstream of the RANBP17 gene[3]. RANBP17 is very close to TLX3 and although its expression is not affected by the translocation, TLX3 expression is affected. The t(5;14)(q35;q32) translocation is found in approximately 20% of childhood T-ALL and 13% of adult cases. Rarer TLX3 rearrangements have also been reported: a t(5;7)(q35;q21) translocation involving CDK6 at 7q21 and a t(5;14)(q35;q11) translocation involving TRA/D at 14q11.2[1].

**

REFERENCES

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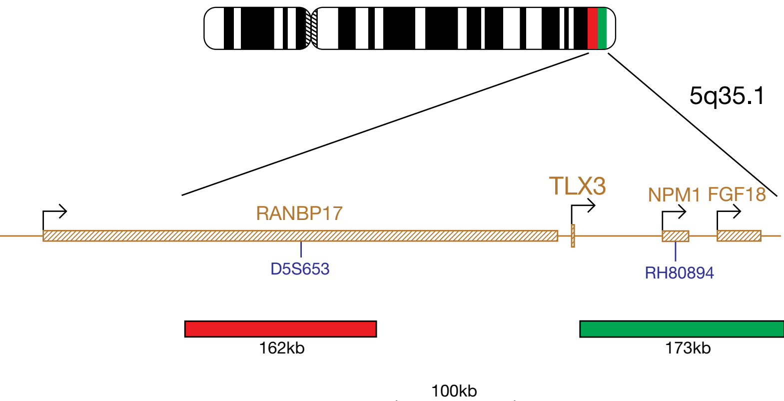

CMP-H051 v002

IVD: *In Vitro* Diagnostic Medical Device
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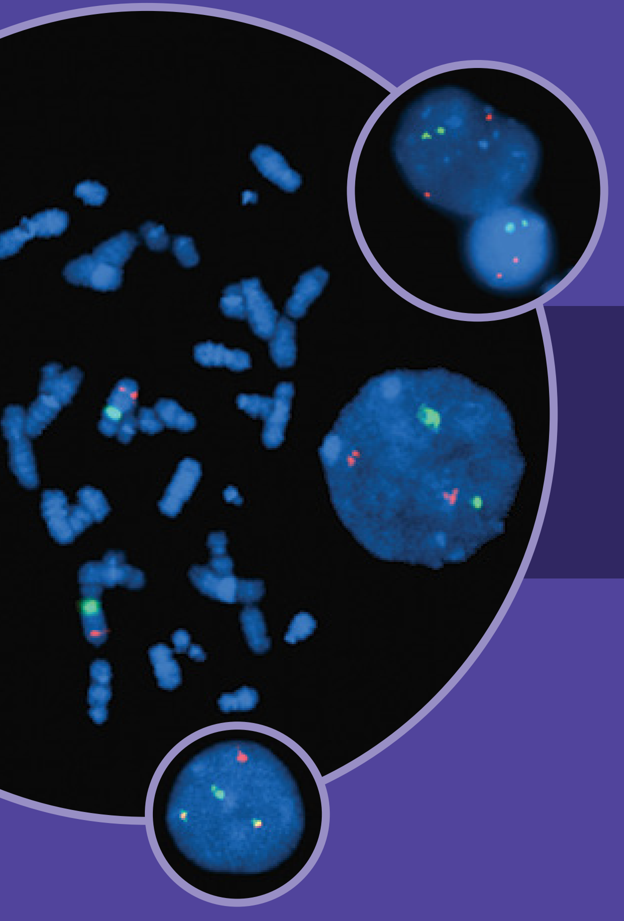

Multiprobe Haematology

Contents

Cytocell FISH probes are CE marked IVDs* unless otherwise indicated.

68 Chromoprobe Multiprobe® ALL v2
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72 Chromoprobe Multiprobe® AML/MDS

Multiprobe Haematology

The Chromoprobe Multiprobe® System is an extension of Cytocell's proprietary Chromoprobe® technology, whereby DNA FISH probes are reversibly bound to the surface of a glass device. These probes dissolve back into solution once in contact with the supplied hybridisation buffer, whilst denaturation of the probes and target DNA occurs simultaneously under the device once heated. This approach not only simplifies the whole FISH procedure but also renders it safer and quicker to use.

This system allows multiple FISH probes to be hybridised on the same slide in a spatially separated manner allowing rapid screening of a patient sample for a number of different DNA sequences in a single FISH analysis.

The assay is supplied in a kit format of 2, 5 or 10 devices and includes hybridisation solution, DAPI counterstain, template slides, a hybridisation chamber and full instructions for use. The kit even contains a unique liquid crystal display slide surface thermometer for accurate temperature measurement of the denaturation surface.

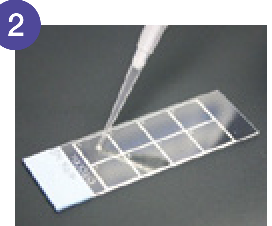
IVD: *In Vitro* Diagnostic Medical Device

The procedure is simple:

1

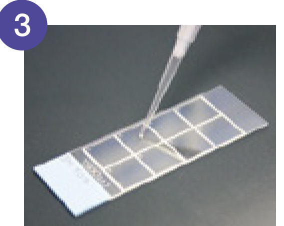
Soak the slides in 100% methanol, then polish dry with a lint free cloth.

2



Spot 4µl of cell sample onto alternate squares of the supplied slide.

3

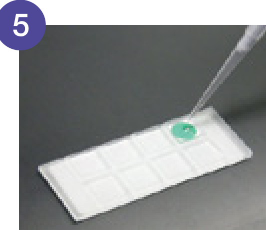


Once dry, fill in the remaining squares with the cell sample and check using phase contrast.

4

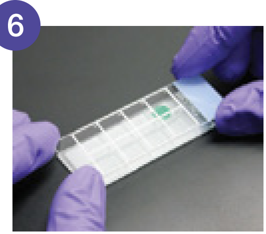
Place slides in 2xSSC for 2 minutes and then dehydrate through an ethanol series.

5



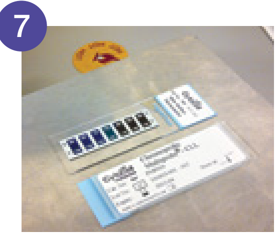
Spot 2µl of supplied hybridisation solution onto each square of the device.

6



Carefully lower spotted slide onto the device.

7



Check the temperature of the hotplate using the slide surface thermometer provided. Denature the slide/device at 75°C for 2 minutes.

8

Place slide/device in hybridisation chamber supplied and float on the surface of a clean 37°C waterbath overnight.

9

Wash in 0.4xSSC at 72°C for 2 minutes, then 2xSSC/0.05% Tween at room temperature for 30 seconds.

10

Apply DAPI counterstain provided, add a coverslip, and view under a fluorescence microscope.

Cytocell multiprobe

Cat. No. **PMP 030**	(2 devices)	Cat. No. **PMP 032**	(10 devices)
Cat. No. **PMP 031**	(5 devices)	Cat. No. **PMP 033**	(20 devices)

Chromoprobe Multiprobe® ALL v2

cMYC (MYC) Breakapart

Chromosomal rearrangements involving the MYC (*MYC proto-oncogene, bHLH transcription factor*) gene at 8q24 are recognised recurrent abnormalities commonly seen in patients with B-cell malignancy. MYC rearrangements, activating MYC by translocation with one of the three immunoglobulin loci (IGH, IGL or IGK), are detected in almost all cases of Burkitt lymphoma at diagnosis[1].

TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion

The cytogenetically-cryptic t(12;21)(p13;q22) translocation between ETV6 *(ETS variant transcription factor 6)* at 12p13 and RUNX1, (*RUNX family transcription factor 1*) at 21q22, results in the ETV6-RUNX1 chimeric fusion gene[2]. This is the most common rearrangement in childhood B-cell acute lymphoblastic leukaemia (B-ALL) accounting for about 25% of cases. B-ALL with ETV6-RUNX1 is considered to have a favourable outcome with cure rates up to 90%. Late relapses have been reported[3].

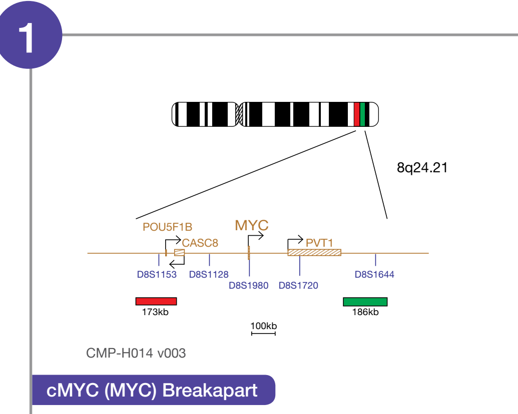
P16 (CDKN2A) Deletion

The CDKN2A (*cyclin dependent kinase inhibitor 2A*) gene at 9p21 is a tumour suppressor gene that has been shown to be deleted in a wide range of human malignancies. Deletions of 9p that include the CDKN2A gene are frequently reported in patients with ALL: in approximately 30% of adult B-cell ALLs, 30% of childhood ALLs and up to 50% of T-cell ALLs. In adult B-ALL, CDKN2A deletions are frequently acquired in disease progression[4,5,6,7].

MLL (KMT2A) Breakapart

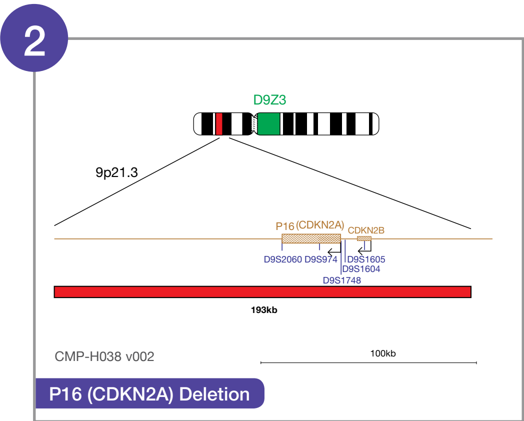
KMT2A rearrangements can be detected in approximately 80% of infants with acute lymphoblastic leukaemia (ALL) and in 5-10% of paediatric and adult ALLs[8,9]. Historically, KMT2A rearrangements in acute leukaemia were associated with a poorer outcome, but recent studies have shown that the prognosis is highly dependent on the fusion partner and it may differ between children and adults[10].

1



cMYC (MYC) Breakapart

2



P16 (CDKN2A) Deletion

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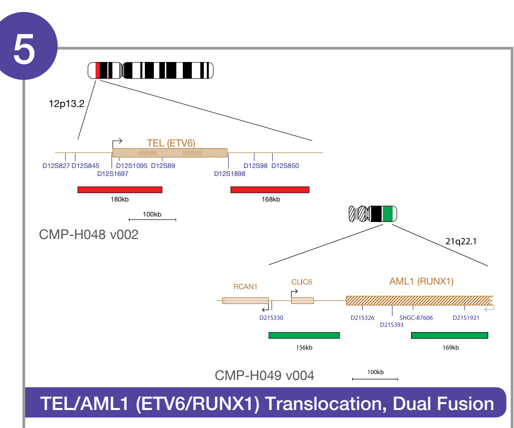
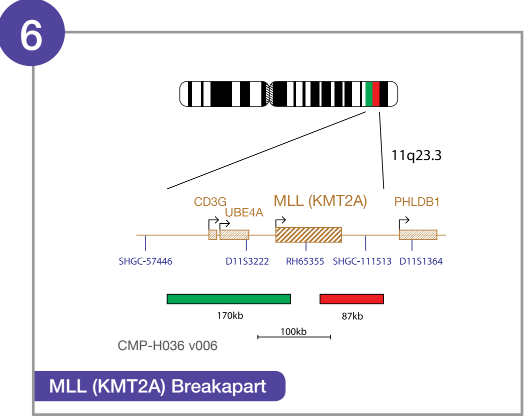


TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion

6



MLL (KMT2A) Breakapart

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E2A (TCF3) Breakapart

The TCF3 (*transcription factor 3*) gene is located at 19p13.3. Translocations involving TCF3 are some of the most common rearrangements in childhood B-ALL. The t(1;19)(q23;p13) is the most common TCF3 rearrangement, being present in around 6% of childhood B-ALL[3,8]. The translocation was historically associated with a poor outcome, though modern intensive therapies have overcome this[3,8,11]. The t(17;19)(q22;p13.) is a rare translocation that is present in around 1% of precursor B-ALL cases[8]. TCF3/HLF positive leukaemia is associated with adverse prognosis[2,11].

BCR/ABL (ABL1) Translocation, Dual Fusion

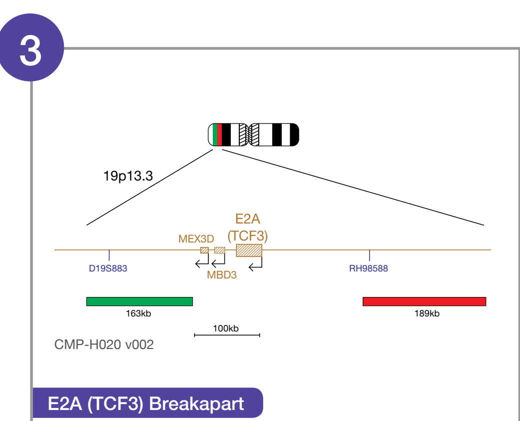
BCR/ABL1 positive ALL has been shown to confer a poor prognosis in both adults and children, thus detection of the abnormality is of high importance for high risk stratification and for treatment and management decisions[12]. In a small number of ALL cases, the translocation does not result in a cytogenetically visible Philadelphia chromosome. In these cases FISH is essential for highlighting the fusion gene[13].

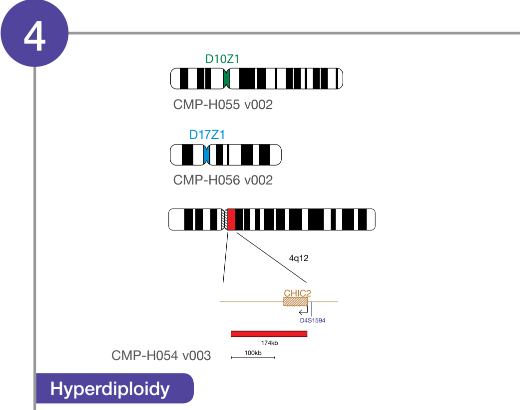
Hyperdiploidy

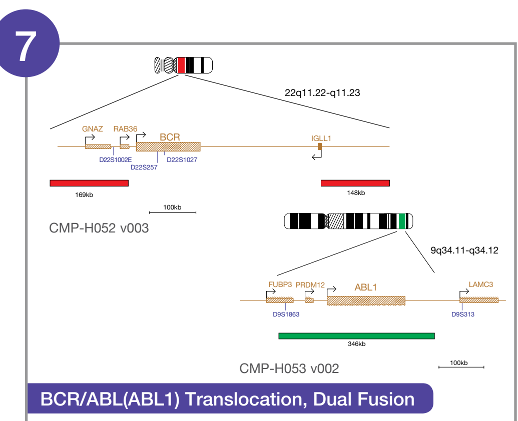
High hyperdiploidy leukaemia (51 – 65 chromosome) is very common in children accounting for about 30% of cases of ALL. It is usually characterised by the gain of specific chromosomes (usually gains of 4,6,10,14, 17,18,21 and X) and is associated with a favourable outcome[3,12,14].

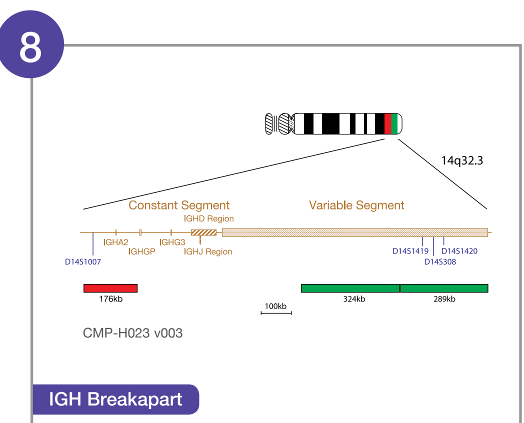
IGH Breakapart

Recurrent rearrangements involving the IGH (*immuno-globulin heavy locus*) gene at 14q32.33 with a wide range of partner genes are seen in haematological malignancies such as ALL[15]. The breakapart design for this probe set allows the detection of rearrangements of the IGH region, regardless of partner gene or chromosome involved.









IVD: *In Vitro* Diagnostic Medical Device

For a list of references, please see page 74.
For more information please see individual product pages.

Cytocell multiprobe

Cat. No. **PMP 018** (2 devices) Cat. No. **PMP 016** (10 devices)
Cat. No. **PMP 017** (5 devices) Cat. No. **PMP 020** (20 devices)

Chromoprobe Multiprobe® CLL

MYB Deletion

The long arm of chromosome 6 (6q) is frequently involved in chromosomal abnormalities in human cancer, including chronic lymphocytic leukaemia (CLL)[1]. The MYB (*MYB proto-oncogene, transcription factor*) is provided as a marker for 6q deletion.

Chromosome 12 Enumeration

Trisomy 12 is a recurrent abnormality in CLL, seen in 20% of cases[3] that often appears as the unique cytogenetic aberration (40-60% of cases with trisomy 12)[2]. Patients with trisomy 12 are classified as low-risk in the absence of any other genetic lesions[4].

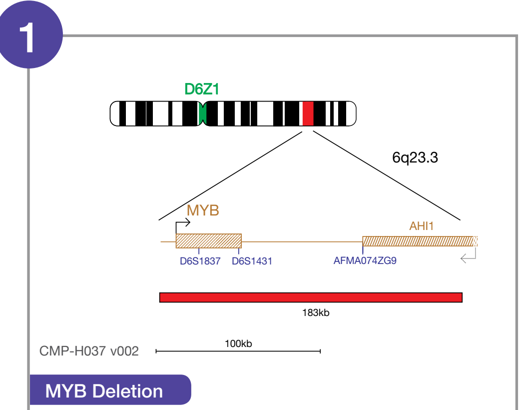
IGH Breakapart

Around 4-9% of CLL patients have a balanced translocation involving IGH. The two most common translocations are IGH/BCL2, caused by the t(14;18) translocation, and IGH/BCL3, a result of the t(14;19) translocation. The prognostic outcome of the translocation is depended on the translocation partner of IGH[2].

P53 (TP53) Deletion

The TP53 (*tumor protein p53*) gene at 17p13 is one of most important tumour suppressor genes; it acts as a potent transcription factor with fundamental role in the maintenance of genetic stability. Loss of TP53 is reported in 10% of patients with CLL, and is considered to be the poorest prognostic marker[4,5].

1



MYB Deletion

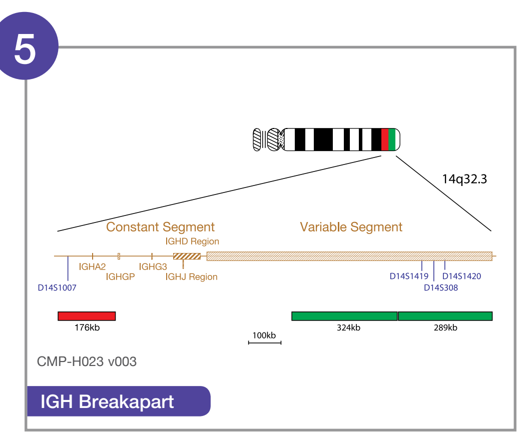
2

D12Z3

CMP-H002 v002

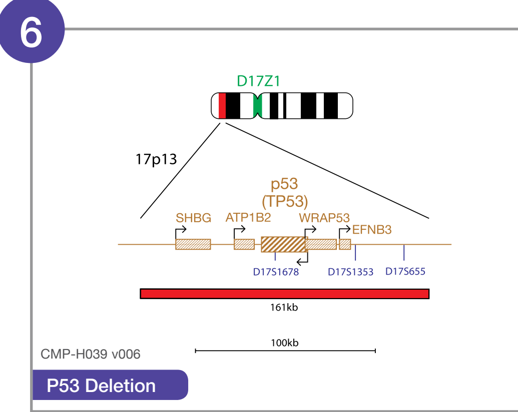
Chromosome 12 Enumeration

5



IGH Breakapart

6



P53 Deletion

IVD: *In Vitro* Diagnostic Medical Device

ATM Deletion

The ATM (*ATM serine/threonine kinase*) gene at 11q22.3 is an important checkpoint gene involved in the management of cell damage and its function is to assess the level of DNA damage in the cell and attempt repair by phosphorylating key substrates involved in the DNA damage response pathway[6]. Loss of ATM is reported in 18% of patients with CLL, and is considered a poor prognostic marker in CLL[7].

IGH/CCND1 Translocation, Dual Fusion

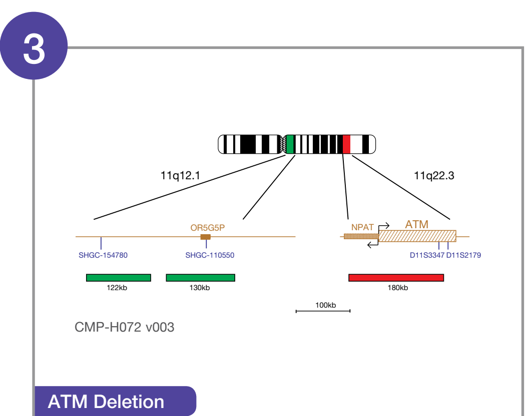
The t(11;14)(q13;q32) rearrangement involving CCND1 and IGH is considered the hallmark of mantle cell lymphoma (MCL)[8], the presence of which can be used to aid in the differential diagnosis of CD5+ B-cell lymphoproliferative disorders[9].

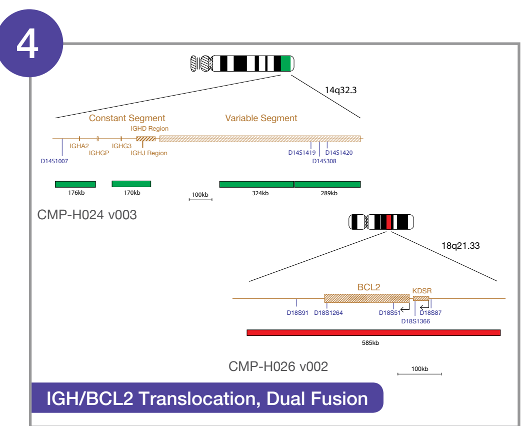
IGH/BCL2 Translocation, Dual Fusion

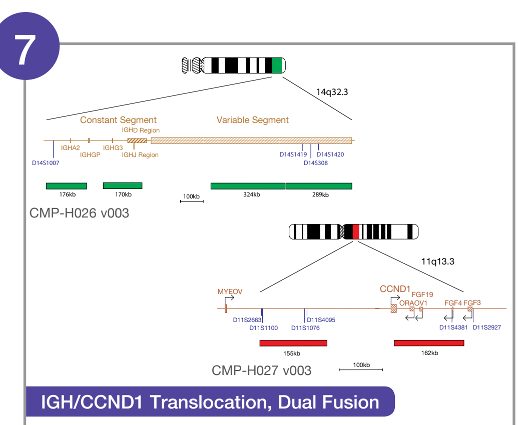
The t(14;18)(q32;q21) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32 and the BCL2 (*BCL2 apoptosis regulator*) gene at 18q21.33 is a recognised recurrent abnormality seen in B-cell malignancies, occurring occasionally in CLL[10].

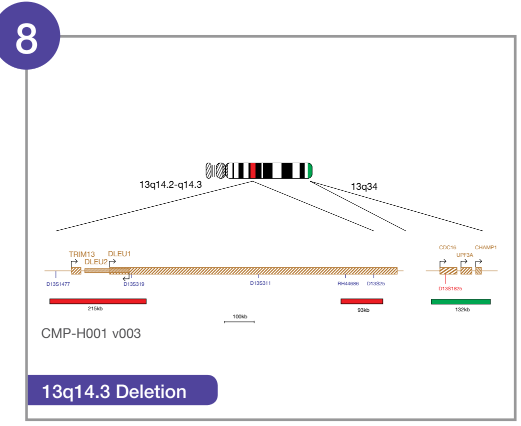
13q14.3 Deletion

Deletions affecting 13q14 are the most frequent structural genetic aberrations in CLL[2,11,12]. This region is found to be heterozygously deleted in 30-60% and homozygously deleted in 10-20% of CLL patients[13]. Patients with 13q14 deletions are classified as very low risk, in the absence of any other genetic lesions[4].









IVD: *In Vitro* Diagnostic Medical Device

For a list of references, please see page 74.
For more information please see individual product pages.

Cytocell multiprobe

Cat. No. **PMP 025**	(2 devices)	Cat. No. **PMP 027**	(10 devices)
Cat. No. **PMP 026**	(5 devices)	Cat. No. **PMP 028**	(20 devices)

Chromoprobe Multiprobe® AML/MDS

Del(5q) Deletion

Deletions of the long arm of chromosome 5 are one of the most common karyotypic abnormalities in myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) with myelodysplasia related changes[1,2]. This del(5q) probe will detect deletions of EGR1 (*early growth response 1*), a tumour suppressor gene at 5q31. EGR1 has been shown to act through haploinsufficiency to initiate the development of MDS/AML[3].

MLL (KMT2A) Breakapart

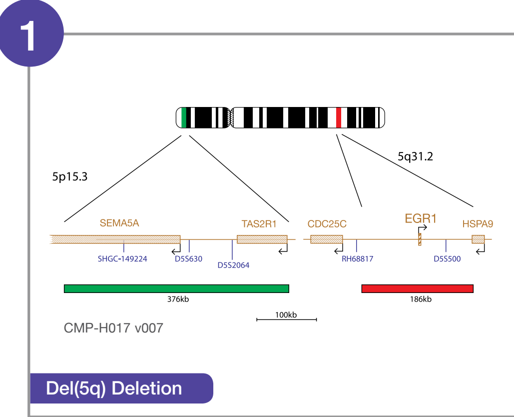
KMT2A rearrangements can be detected in approximately 60% of infant AML and in 3% of *de novo* and 10% of therapy related adult AML cases[4,5]. Historically, KMT2A rearrangements in acute leukaemia were associated with a poorer outcome, but recent studies have shown that the prognosis is highly dependent on the fusion partner and it may differ between children and adults[6].

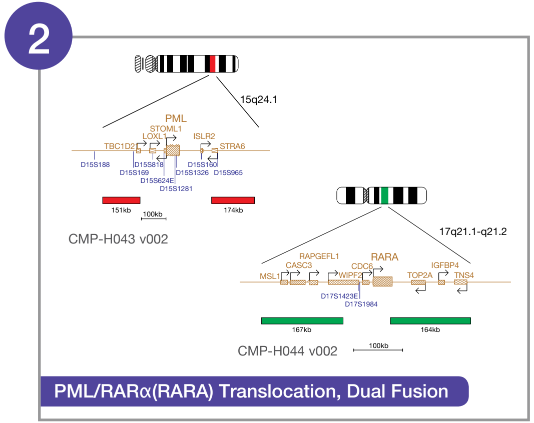
PML/RARα(RARA) Translocation, Dual Fusion

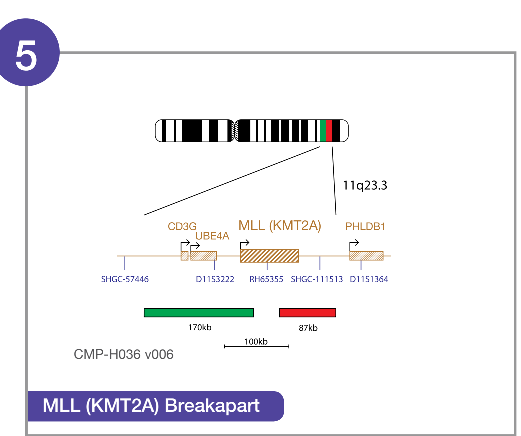
The translocation t(15;17)(q24;q21) gives rise to the PML-RARA fusion gene and is the diagnostic hallmark of acute promyelocytic leukaemia (APL). Immediate treatment of APL patients is critical, due to fatal coagulation disorders and life-threatening haemorrhage in diagnosis. Since the introduction of all-trans-retinoic-acid (ATRA) and arsenic trioxide (ATO) in APL treatment protocols, the overall survival rate has improved dramatically, with nearly 90% of patients cured[7,8].

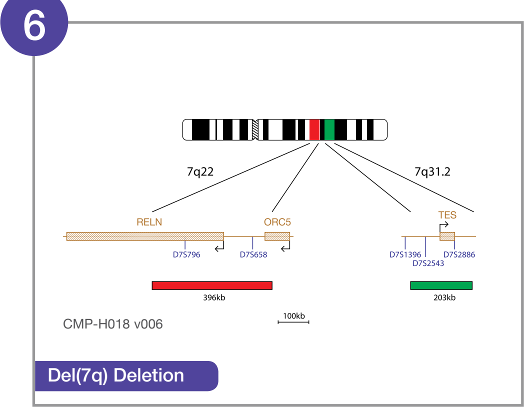
Del(7q) Deletion

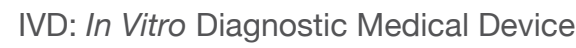
Monosomy of chromosome 7 and deletions of the long arm of chromosome 7 are recognised recurrent chromosomal aberrations frequently seen in myeloid malignancies and are associated with poorer outcome[9,10].










IVD: *In Vitro* Diagnostic Medical Device

P53 (TP53) Deletion

The TP53 (*tumor protein p53*) gene at 17p13 is one of the most important tumour suppressor genes; it acts as a potent transcription factor with a fundamental role in the maintenance of genetic stability. In AML and acute lymphoblastic leukaemia (ALL), TP53 loss is associated with a poor outcome and is often seen as a marker of disease progression or secondary disease[11,12].

AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion

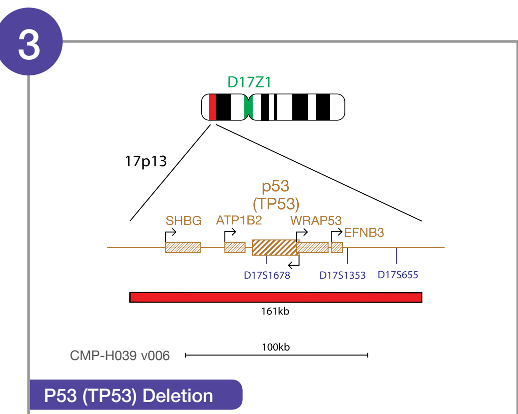
The translocation t(8;21)(q22;q22) gives rise to the RUNX1-RUNX1T1 fusion gene. The translocation is observed in 10-22% of patients with AML FAB type M2 and 5-10% of AML cases overall, most commonly in children and young adults[15] and is a good prognostic indicator[11,16,17].

CBFβ (CBFB)/MYH11 Translocation, Dual Fusion

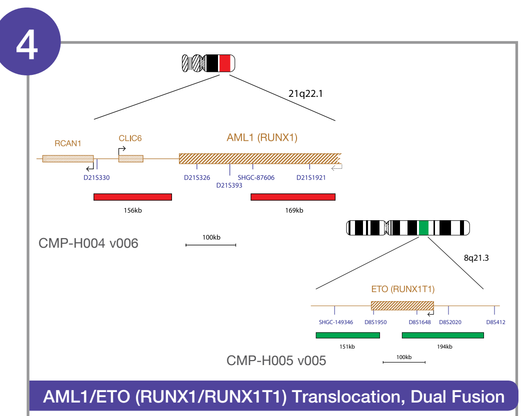
The inversion inv(16)(p13.1q22.1) and the translocation t(16;16)(p13.11;q22.1) give rise to the CBFB-MYH11 fusion gene. These rearrangements are frequently found in patients with a myelomonocytic subtype with increased bone marrow eosinophils, AML FAB (French-American-British classification) type M4Eo, and are found in 5-8% of all AMLs. Cases of therapy-related AML may also have this rearrangement[2,13]. CBFB-MYH11 rearrangements are classed as a favourable cytogenetic risk group in patients with AML[11,14].

Del(20q) Deletion

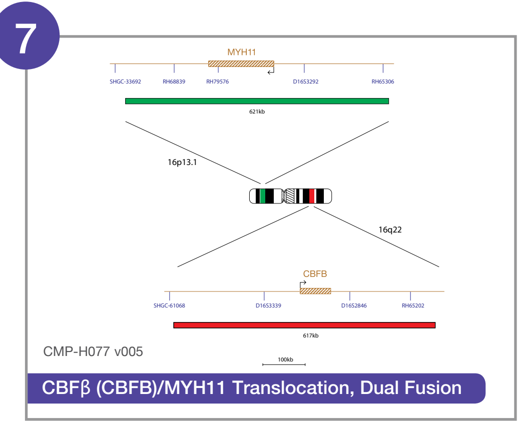
Deletions of the long arm of chromosome 20 are a common chromosomal abnormality associated with myeloid malignancies, in particular myelodysplastic syndromes (MDS) and AML[18]. Deletions of 20q can be seen in 4% of MDS cases and in 1-2% of AML cases[19]. The prognosis for MDS where del(20q) is the sole abnormality is good; however, the presence of secondary abnormalities may be indicative of disease progression[20].



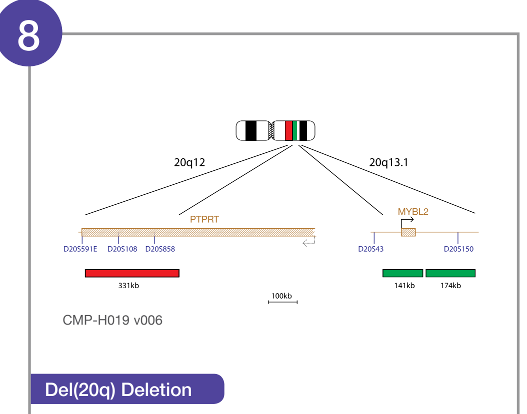
P53 (TP53) Deletion



AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion



CBFβ (CBFB)/MYH11 Translocation, Dual Fusion



Del(20q) Deletion

IVD: *In Vitro* Diagnostic Medical Device

For a list of references, please see page 74.
For more information please see individual product pages.

CHROMOPROBE MULTIPROBE® ALL: REFERENCES PAGES 68-69

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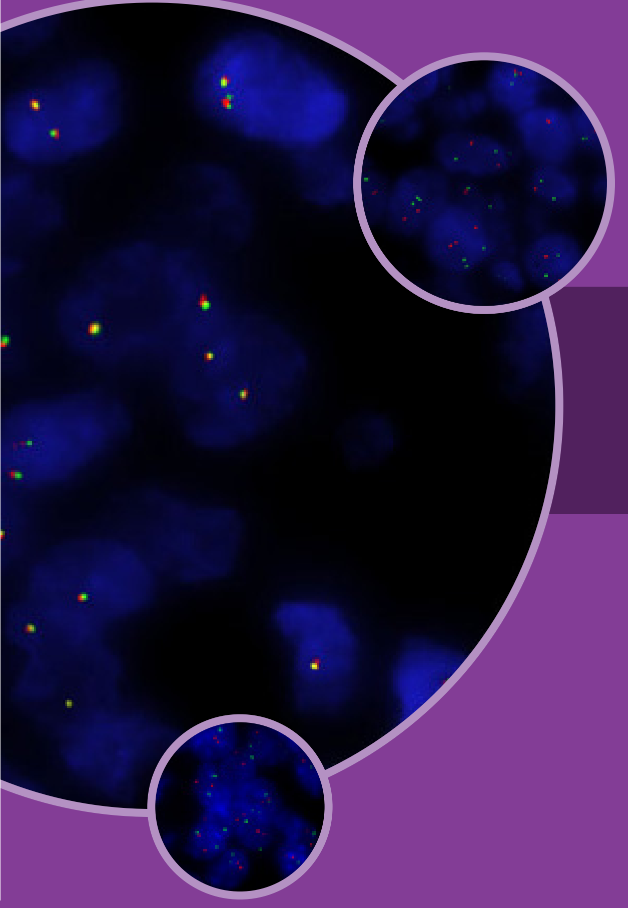

Haematopathology

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Haematopathology

The assessment of genetic changes in tissue biopsies can provide important information for prediction of tumour progression. The majority of these changes are either amplifications, deletions or other chromosomal rearrangements that can be detected using FISH.

Current methodologies, namely immunohistochemistry or blotting techniques, can provide information at the gene expression level but, when carried out on tissue sections (either cryostat or paraffin embedded), FISH can provide information at the DNA level, *in situ*, at the precise site within the tumour. This can reveal cell-to-cell heterogeneity and enable the detection of small clones of genetically distinct cells. This analysis can be made even more efficient through the use of automated image analysis systems and software.

IVD: *In Vitro* Diagnostic Medical Device

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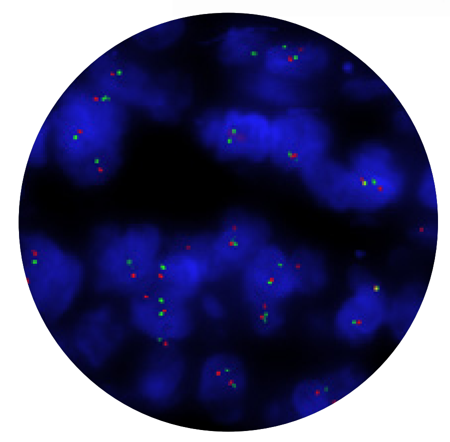
Cat. No. **LPS 028** (10 tests)

BCL2 Breakapart



The BCL2 (*BCL2 apoptosis regulator*) gene located at 18q21.33 encodes one member of a large protein of a large protein family that regulates and contributes to programmed cell death, or apoptosis, by controlling mitochondrial membrane permeability[1].

Translocations of the BCL2 gene result in constant expression of the BCL2 protein; these most frequently involve the immunoglobulin (IG) heavy chain (IGH) gene via a t(14;18)(q32.33;q21.33) translocation or, more rarely, involve the IG light chain (IGK or IGL) loci via t(2;18)(p11.2;q21.33) or t(18;22)(q21.33;q11.2) translocations[2].

The t(14;18)(q32.33;q21.33) translocation is thought to be brought about by an error in the joining function of the IGH gene, mediated by the observation that both IGH and BCL2 are arranged next to each other in 3D space in normal B lymphocytes[3]. The translocation breakpoint at the end of the Joining (J) segment, and the subsequent fusion of the BCL2 gene to this region, results in the BCL2 gene coming under the regulatory control of those processes normally involved in maintenance of IGH gene activity[4].

The t(14;18)(q32.33;q21.33) translocation is observed in 70-95% of follicular lymphoma (FL) cases and 20-30% of diffuse large B-cell lymphoma (DLBCL)[2]. Presence of the t(14;18) translocation in DLBCL is a predictor of outcome and has a poor prognostic effect[5]. BCL2 translocations have also been implicated in chronic B-cell lymphoproliferative disease (CLPD) and also occur occasionally in chronic lymphocytic leukaemia (CLL)[6].

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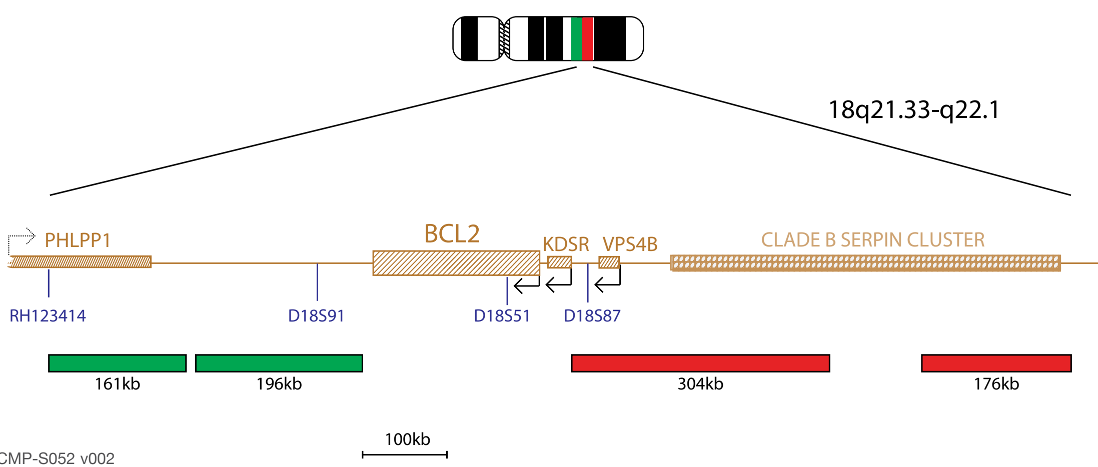
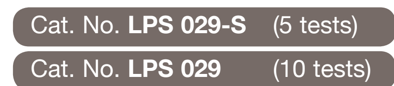


CMP-S052 v002

IVD: *In Vitro* Diagnostic Medical Device



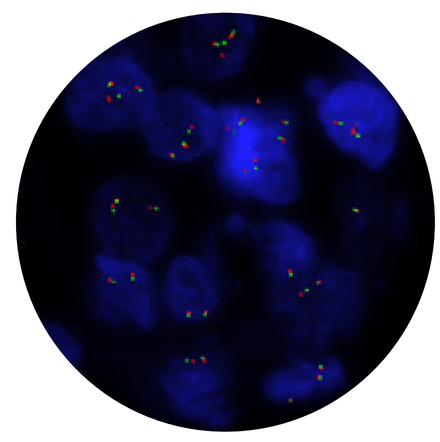
BCL6 Breakapart*

Chromosomal rearrangements involving the BCL6 (*BCL6 transcription repressor*) gene at 3q27 are recognised recurrent abnormalities commonly seen in patients with B-cell malignancy[1].

BCL6 rearrangements are the most common chromosomal abnormalities seen in diffuse large B-cell lymphoma (DLBCL), occurring in up to 35% of cases[2]. They are also seen frequently in follicular lymphoma, where they occur in up to 15% of cases[3]. BCL6 is expressed in normal germinal centre B-cells and follicle helper T-cells. BCL6 translocations alter expression by promoter substitution and cause deregulated expression of normal BCL6 protein[1,4].

Approximately 50% of BCL6 translocations will involve one of the three immunoglobulin loci (IGH, IGL or IGK); the remainder of translocations involve one of more than twenty different non-immunoglobulin genes[5]. Additionally, gains and amplifications of the BCL6 gene have also been reported in cases of B-cell lymphoma[6].

The presence of concurrent BCL6 rearrangements with MYC and/or BCL2 rearrangements in patients with 'dual-hit' lymphoma has been shown to be associated with aggressive disease[7].



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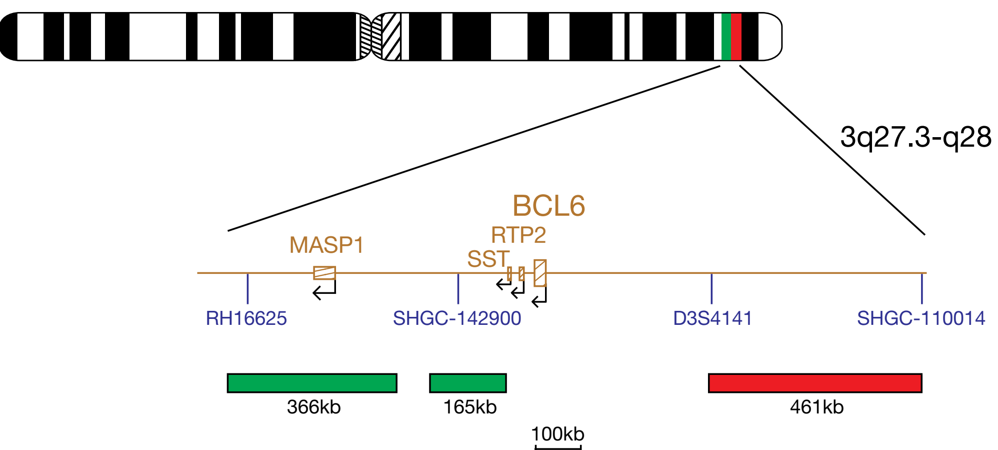

CMP-S047 v002

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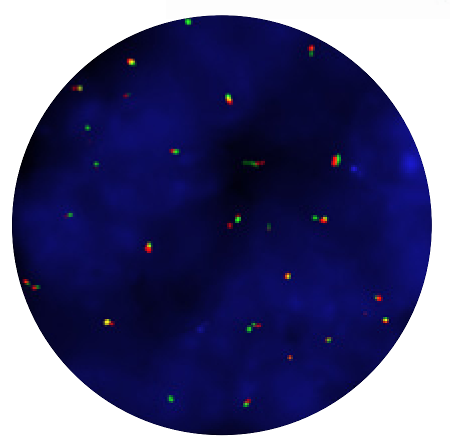
IVD: *In Vitro* Diagnostic Medical Device

CCND1 Breakapart



Rearrangements involving the CCND1 (*cyclin D1*) region at 11q13.3 are seen in a variety of tumour types.

The t(11;14)(q13;q32) rearrangement involving CCND1 and IGH is considered the hallmark of mantle cell lymphoma (MCL)[1], the presence of which can be used to aid in the differential diagnosis of CD5+ B-cell lymphoproliferative disorders[2].

A similar t(11;14) translocation is also seen in 15% patients with multiple myeloma[3,4], where it appears to be associated with a favourable outcome in most series and is regarded as neutral with regard to prognosis[5].

Amplification of the CCND1 region has been reported in a number of solid tumours including breast cancer[6], squamous cell carcinoma[7] and gastric cancer[8].

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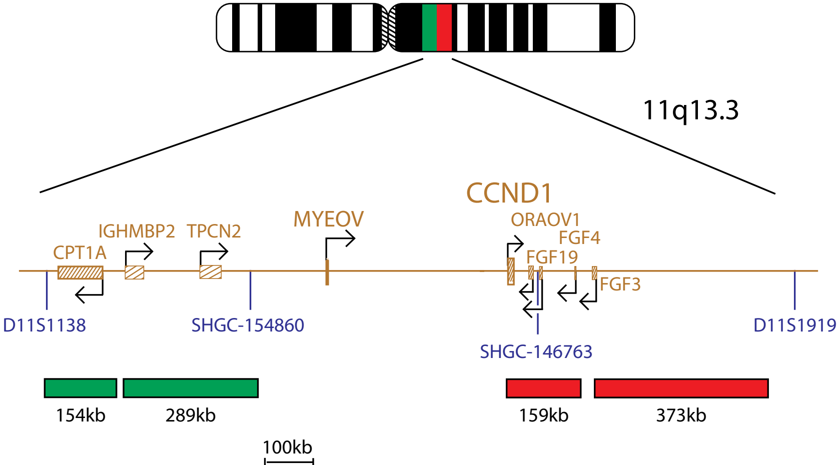

CMP-S048 v002

IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

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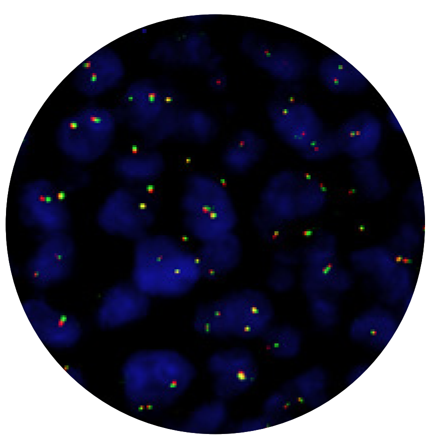
Cat. No. **LPS 032** (10 tests)

IGH Breakapart*



Recurrent rearrangements involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.33 with a wide range of partner genes are seen in lymphomas and haematological malignancies[1].

A t(8;14)(q24;q32) translocation, involving IGH and the MYC gene at 8q24, is frequently seen in Burkitt lymphoma[2] and diffuse large B-cell lymphoma (DLBCL)[3]. Other rearrangements frequently reported in B-cell lymphoma include: the t(14;18)(q32;q21) translocation, involving IGH and the BCL2 gene, seen in both follicular lymphoma and DLBCL[4]; and the t(11;14)(q13;q32) involving IGH and the CCND1 gene, which is the hallmark of mantle cell lymphoma (MCL)[5].

IGH rearrangements with a number of different gene partners are a frequent finding in patients with multiple myeloma, including: t(4;14)(p16;q32) translocations involving IGH with FGFR3 and WHSC1; t(6;14)(p21;q32) translocations involving IGH and CCND3; t(11;14)(q13;q32) translocations involving IGH and CCND1; t(14;16)(q32;q23) translocations involving IGH and MAF, and t(14;20)(q32;q12) translocations involving IGH and MAFB[6,7].

IGH rearrangements are also reported as recurrent abnormalities in patients with lymphoplasmacytic lymphoma (LPL), chronic lymphocytic leukaemia (CLL), extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type and acute lymphoblastic leukaemia (ALL)[8].

The breakapart design for this probe set allows the detection of rearrangements of the IGH region, regardless of partner gene or chromosome involved.

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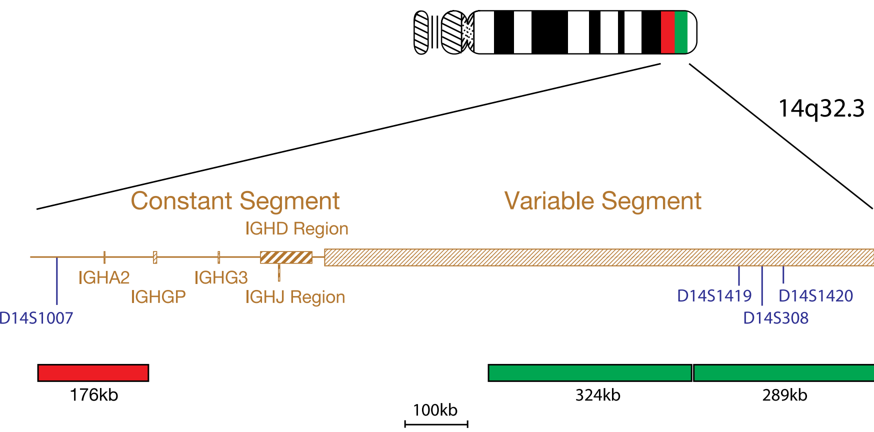


CMP-H023 v003

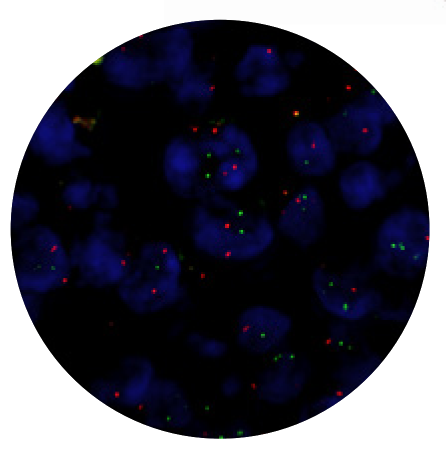
***Similar products are available in the Haematology range, refer to pages 36 and 37.**

IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

Cat. No. **LPS 033-S** (5 tests)
Cat. No. **LPS 033** (10 tests)

IGH/BCL2 Translocation, Dual Fusion*



The t(14;18)(q32;q21) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32.33 and the BCL2 (*BCL2 apoptosis regulator*) gene at 18q21.33 is a recognised recurrent abnormality seen in B-cell malignancies.

IGH-BCL2 rearrangements are observed in 70-95% of follicular lymphoma (FL) cases and 20-30% of diffuse large B-cell lymphoma (DLBCL)[1]. Presence of the t(14;18) translocation in DLBCL is a predictor of outcome and has a poor prognostic effect[2]. BCL2 translocations have also been implicated in chronic B-cell lymphoproliferative disease (CLPD) and also occur occasionally in chronic lymphocytic leukaemia (CLL)[3].

REFERENCES

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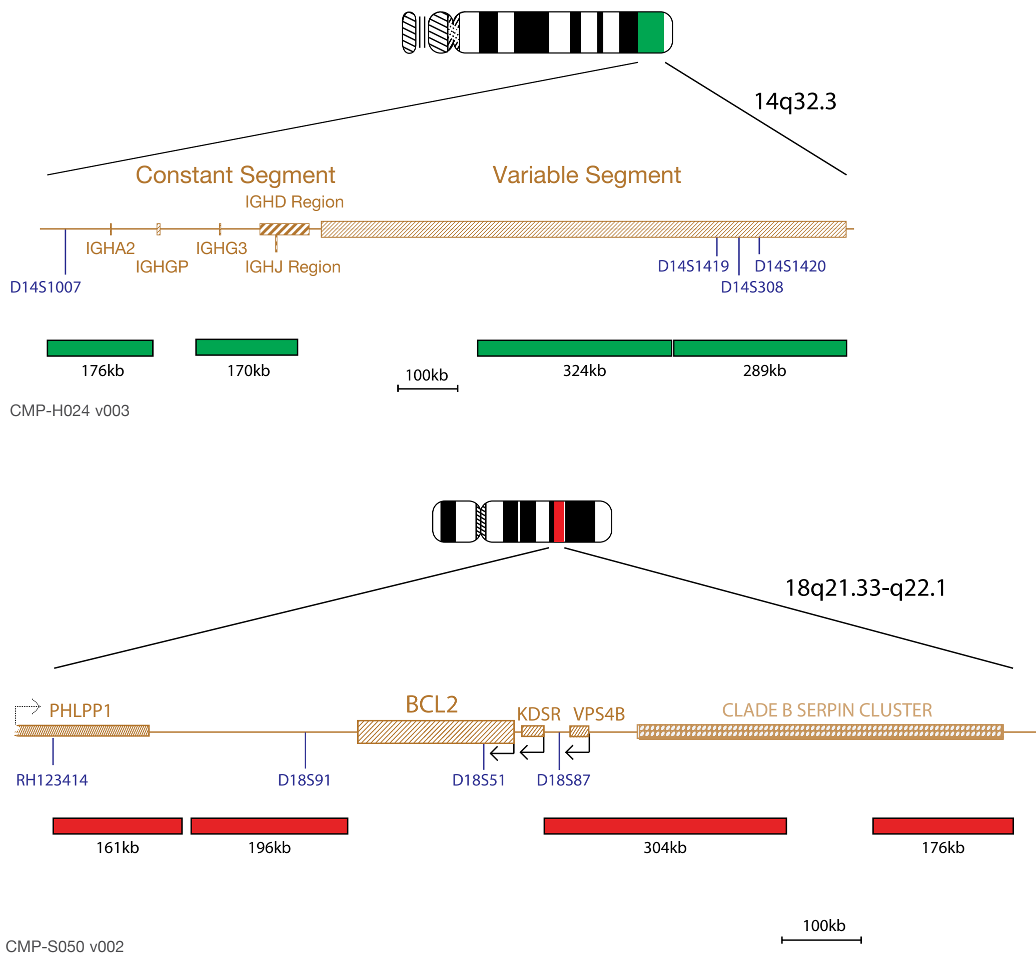

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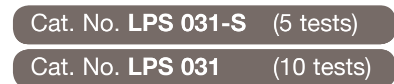
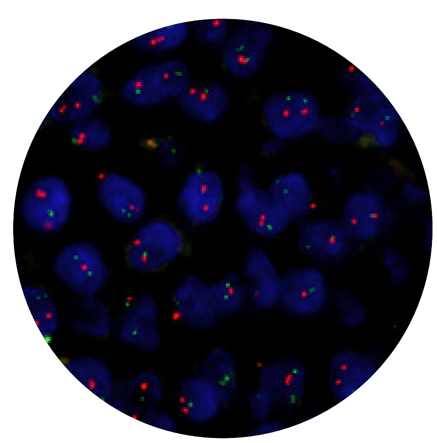
IVD: *In Vitro* Diagnostic Medical Device



IGH/CCND1 Translocation, Dual Fusion*



The t(11;14)(q13;q32) translocation involving CCND1 (*cyclin D1*) gene at 11q13.3 and the IGH (*immunoglobulin heavy locus*) gene at 14q32 is associated with mantle cell lymphoma.

The t(11;14)(q13;q32) rearrangement involving CCND1 and IGH is considered the hallmark of mantle cell lymphoma (MCL)[1], the presence of which can be used to aid in the differential diagnosis of CD5+ B-cell lymphoproliferative disorders[2].

Amplification of the CCND1 region has been reported in a number of solid tumours including breast cancer[3], squamous cell carcinoma[4] and gastric cancer[5].

REFERENCES

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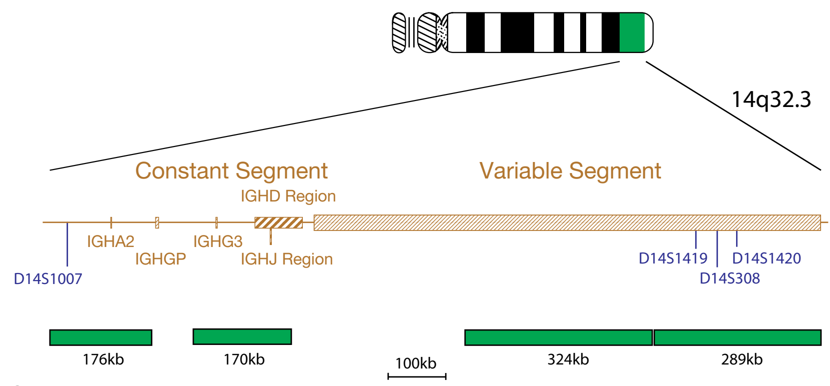
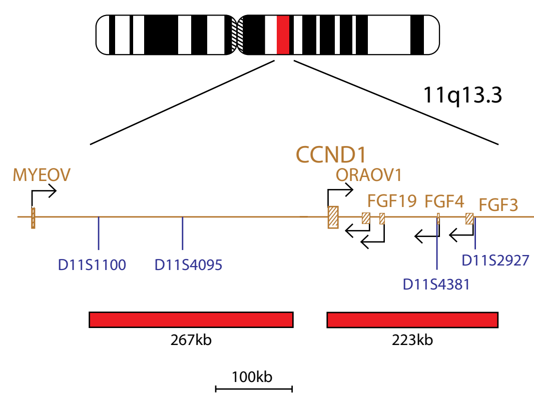
4. Mahdey HM, *et al*. Asian Pac J Cancer Prev 2011;12:2199-204
5. Stahl P, *et al*. BMC Gastroenterol 2015;15:7



CMP-H024 v003



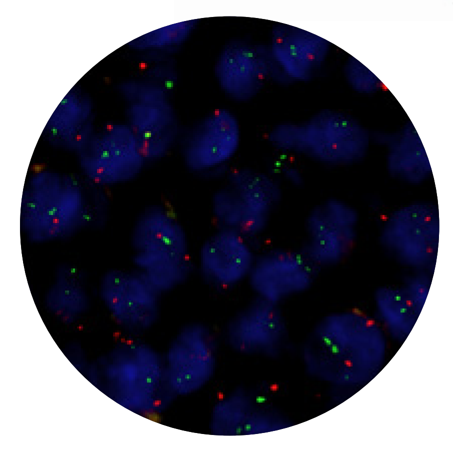
CMP-S053 v002

***A similar product is also available within the Haematology range, refer to page 39.**

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPS 034-S** (5 tests)
Cat. No. **LPS 034** (10 tests)

IGH/MALT1 Translocation, Dual Fusion



The t(14;18)(q32;q21) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32 and the MALT1 (*MALT1 paracaspase*) at 18q21 is a recognised recurrent abnormality seen in MALT lymphoma[1].

Rearrangements of MALT1 are associated with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type and are characterised by two main translocations: the t(11;18)(q21;q21.32) involving the BIRC3 gene and the t(14;18)(q32;q21.32) involving the IGH gene. Other MALT1-associated translocations are rare[1,3].

The t(14;18) translocation is present in approximately 18% of MALT lymphomas and is most frequently found in liver, skin and ocular adnexa sites rare for the t(11;18)[2]. Both translocations result in the constitutive activation of the NF-kappaB pathway[4].

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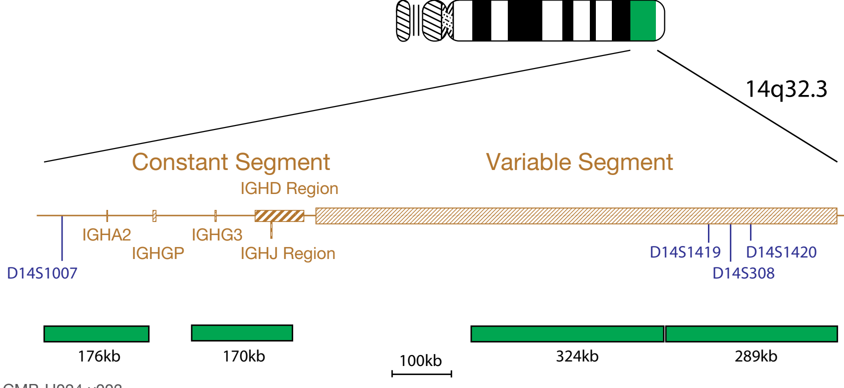

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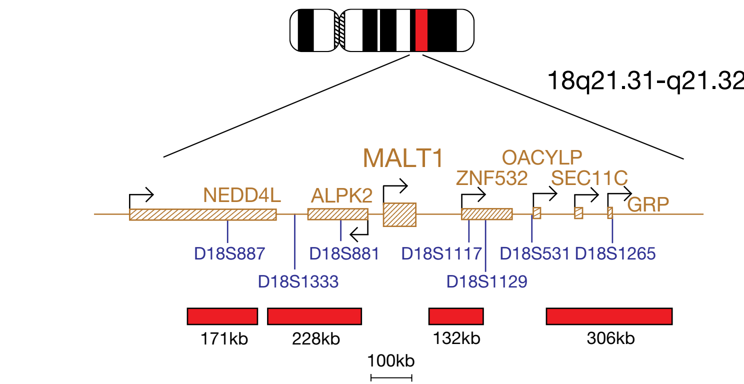

CMP-S054 v002

IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

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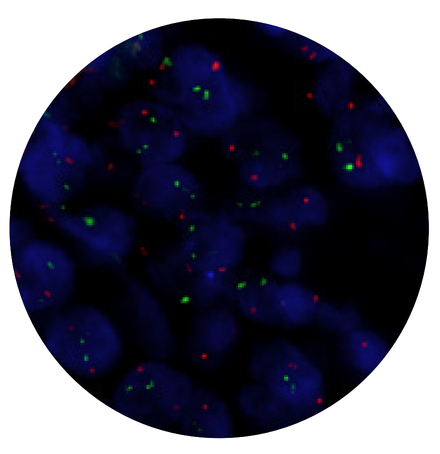
Cat. No. **LPS 035** (10 tests)



IGH/MYC Translocation, Dual Fusion*

The t(8;14)(q24;q32) translocation involving the IGH (*immunoglobulin heavy locus*) gene at 14q32 and the MYC (*MYC proto-oncogene, bHLH transcription factor*) oncogene at 8q24 is a recognised recurrent abnormality commonly seen in patients with B-cell malignancy.

IGH-MYC rearrangements are detected in up to 85% of cases of Burkitt lymphoma at diagnosis[1]. They are also seen in diffuse large B-cell lymphoma (DLBCL)[2], multiple myeloma and plasmablastic lymphoma[3,4].

In an IGH-MYC rearrangement the translocation breakpoints on chromosome 14 are clustered to a narrow region 5' to the intron enhancer of the immunoglobulin heavy chain, whereas the breakpoints on chromosome 8 can occur more than 340kb upstream of MYC, with no preferential site[5]. The translocation brings MYC into close proximity to the IGH enhancer and results in the up-regulation of MYC. Over-expression of the transcription factor stimulates gene amplification, resulting in uncontrolled cell proliferation[6].

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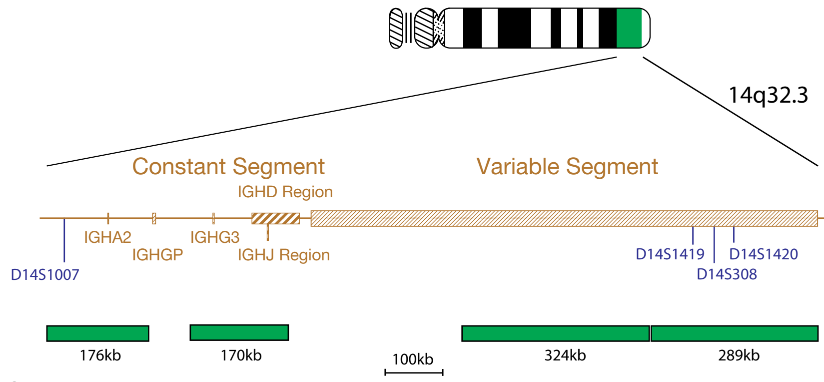

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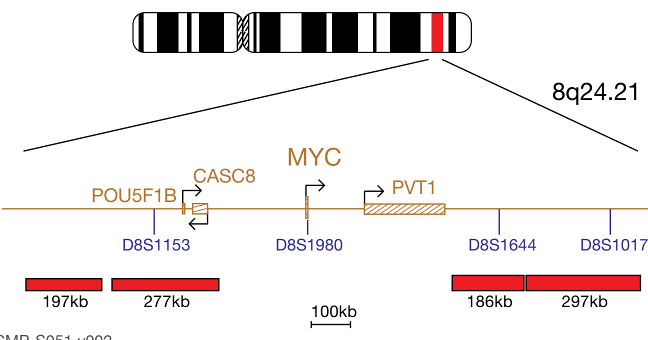


CMP-S051 v002

***A similar product is also available within the Haematology range, refer to page 41.**

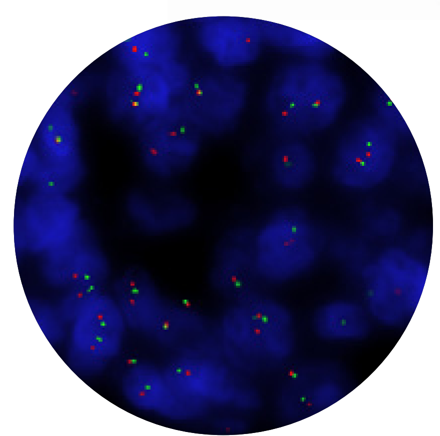
IVD: *In Vitro* Diagnostic Medical Device

IGK Breakapart and IGL Breakapart*

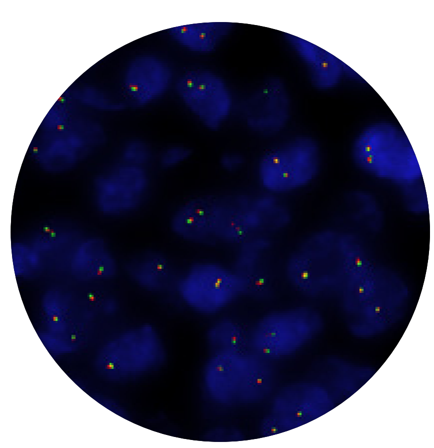
Recurrent rearrangements involving the IGK (*immunoglobulin kappa locus*) gene at 2p11.2 or the IGL (*immunoglobulin lambda locus*) gene at 22q11, with a wide range of partner genes, are seen in lymphomas and haematological malignancies.

A large number of B-cell malignancies harbour translocations involving the immunoglobulin (IG) loci. The majority of cases will show rearrangements involving the IGH gene; however, variant translocations have been described in 5-10% of B-cell neoplasms which involve either the immunoglobulin kappa (IGK) light chain locus at 2p11.2 or the immunoglobulin lambda (IGL) light chain locus at 22q11[1,2].

Variant translocations involving the IG light chain loci are seen in Burkitt lymphoma and multiple myeloma, with the presence of a t(2;8)(p12;q24) MYC-IGK, or t(8;22)(q24;q11) MYC-IGL[3,5]. In diffuse large B-cell lymphoma (DLBCL), translocations may involve the BCL6 gene via t(2;3)(p12;q27) or t(3;22)(q27;q11) translocations, or the BCL2 gene via t(2;18)(p12;q21) or t(18;22)(q21;q11) translocations[6].



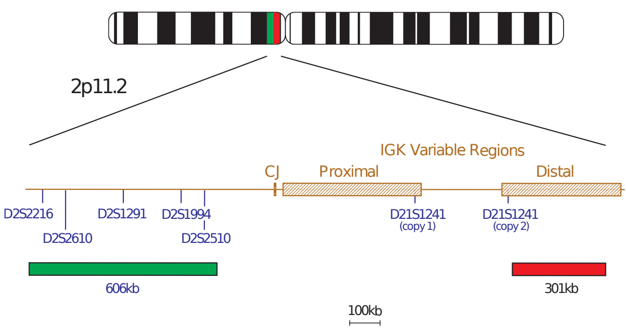
IGK Breakapart



IGL Breakapart

IGK Breakapart

Cat. No. **LPS 038**



CMP-H034 v005

IGL Breakapart

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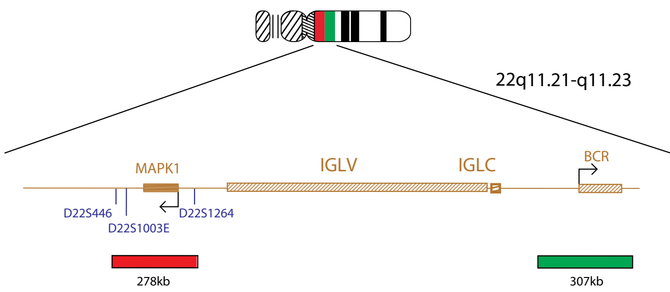

CMP-H035 v004

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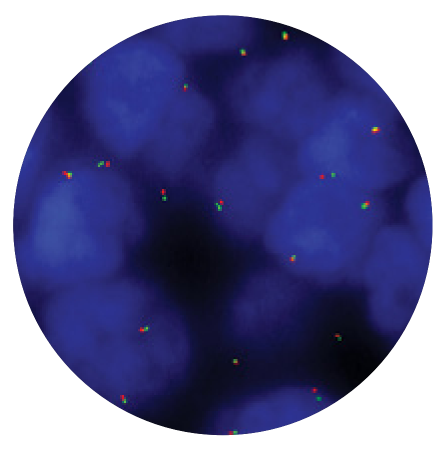
***Similar products are also available within the Haematology range, refer to page 46.**

IVD: *In Vitro* Diagnostic Medical Device

MALT1 Breakapart



The MALT1 (*MALT1 paracaspase*) gene is located at 18q21.

Rearrangements of MALT1 are associated with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type and are characterised by two main translocations: the t(11;18)(q21;q21.32) involving the BIRC3 (baculoviral IAP repeat containing 3) gene and the t(14;18)(q32;q21.32) involving the IGH (*immunoglobulin heavy locus*) gene. Other MALT1-associated translocations are rare[1].

The t(11;18) translocation is present in 18-33% of cases of MALT lymphoma and is most frequently found in pulmonary, gastrointestinal and parotid gland MALT1 lymphomas[1,2,3]; the t(14;18) translocation is present in approximately 18% of MALT lymphomas and is most frequently found in liver, skin, and ocular adnexa - sites rare for the t(11;18)[3]. Both translocations result in the constitutive activation of the NF-kappaB pathway[4].

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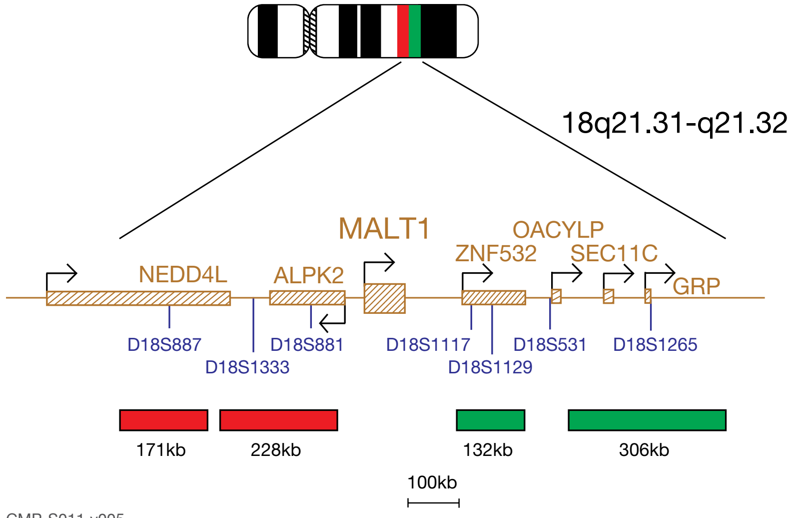

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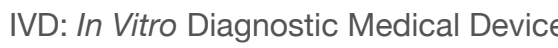
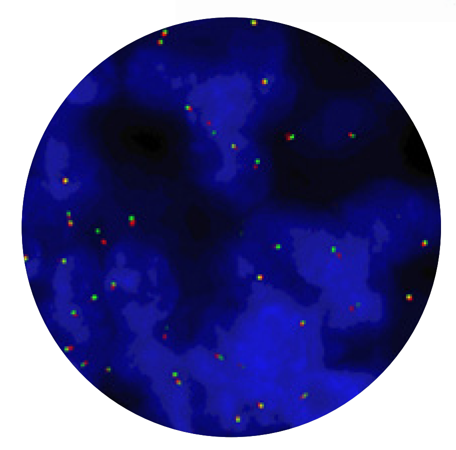

IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

Cat. No. **LPS 027-S** (5 tests)
Cat. No. **LPS 027** (10 tests)

MYC Breakapart*



Chromosomal rearrangements involving the MYC (*MYC proto-oncogene, bHLH transcription factor*) gene at 8q24 are recognised recurrent abnormalities commonly seen in patients with B-cell malignancy.

MYC rearrangements, activating MYC by translocation with one of the three immunoglobulin loci (IGH, IGL or IGK), are detected in almost all cases of Burkitt lymphoma at diagnosis[1]. They are also seen in diffuse large B-cell lymphoma (DLBCL)[2], multiple myeloma and plasmablastic lymphomas[3,4], amongst other diseases.

MYC has also been shown on rare occasions to be involved in rearrangements with a number of non-immunoglobulin partners[5].

The presence of concurrent MYC rearrangements with BCL2 and/or BCL6 rearrangements in patients with 'dual-hit' lymphoma has been shown to be associated with aggressive disease[6].

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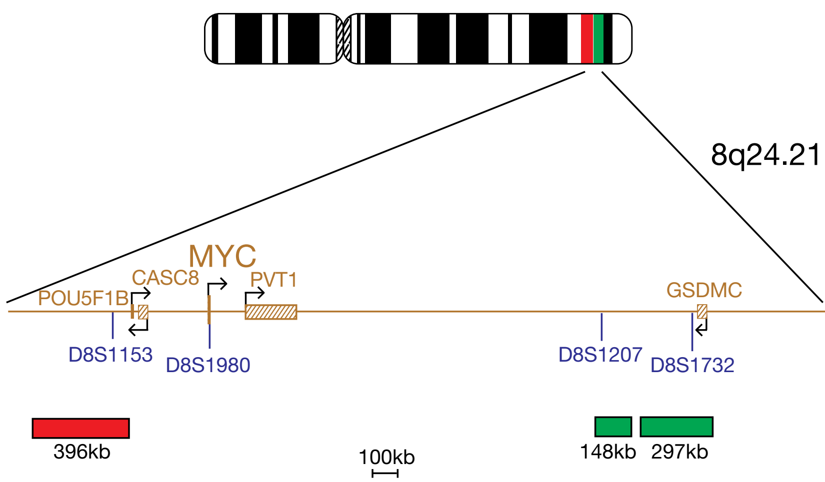

CMP-S049 v003

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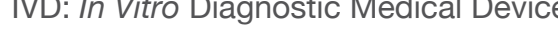
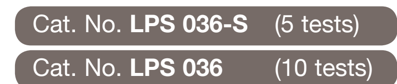
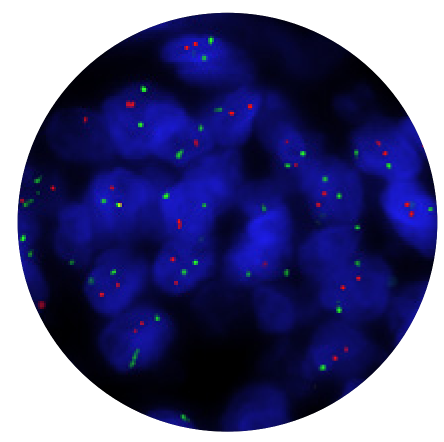
IVD: *In Vitro* Diagnostic Medical Device





P16 (CDKN2A) Deletion*



The CDKN2A (*cyclin dependent kinase inhibitor 2A*) gene at 9p21 is a tumour suppressor gene that has been shown to be deleted in wide range of human malignancies.

Loss of the CDKN2A gene results in cellular proliferation and dysregulation of pro-apoptotic pathways. There are two proteins produced by the CDKN2A gene: $p16^{INK4a}$ and $p14^{ARF}$; these protein products have been linked to two tumour suppressor pathways – the RB pathway and the p53 pathway, respectively[1].

Deletions of 9p that include the CDKN2A gene are frequently reported in patients with acute lymphoblastic leukaemia (ALL): in approximately 30% of adult B-cell ALLs, 30% of childhood ALLs and up to 50% of T-cell ALLs. In adult B-cell ALL, CDKN2A deletions are frequently acquired in disease progression[2,3,4,5].

Deletions including the CDKN2A locus have been reported in up to a third of patients with diffuse large B-cell lymphoma (DLBCL)[6] and, in glioma, CDKN2A loss has been implicated with shorter overall survival in WHO grade I-III astrocytomas[7].

Losses of the CDKN2A region have also been reported in malignant mesothelioma, melanoma, and bladder cancer[8,9,10].

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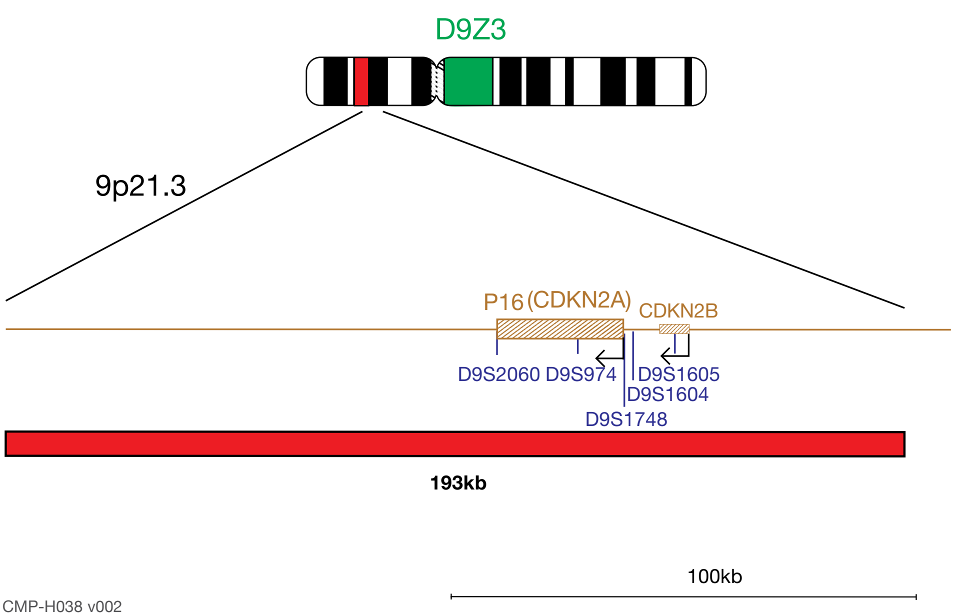

CMP-H038 v002

*A similar product is also available within the Haematology range, refer to page 52.

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPS 037-S** (5 tests)
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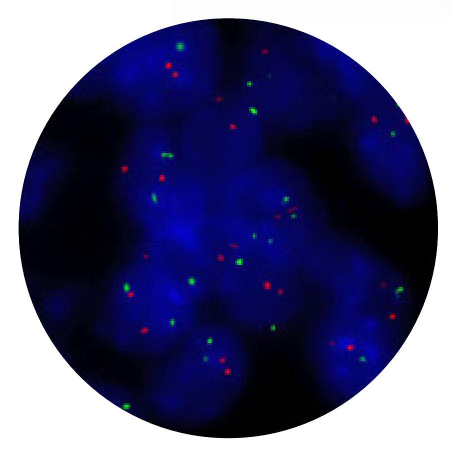


Haematopathology

P53 (TP53) Deletion*

The TP53 (*tumor protein p53*) gene at 17p13.1 is a tumour-suppressor gene that has been shown to be deleted in a wide range of human malignancies.

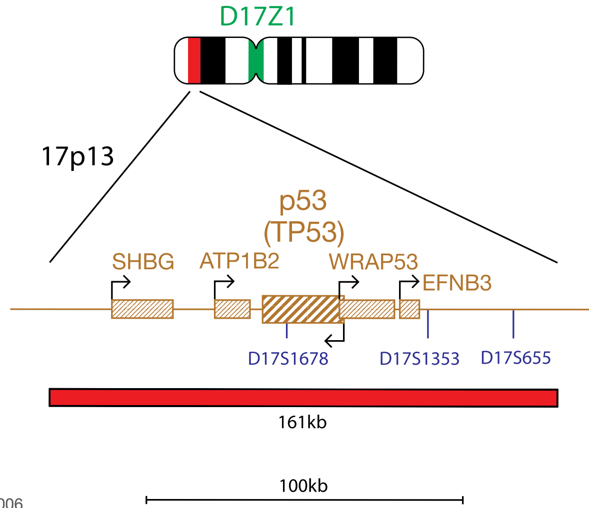
The TP53 gene is one of most important tumour suppressor genes; it acts as a potent transcription factor with a fundamental role in the maintenance of genetic stability. Screening for TP53 loss is important as deletions or losses of the short arm of chromosome 17, which includes the TP53 region, are reported in many cancers and are often associated with disease progression, inferior response to treatment and/or a poor prognosis[1-9].

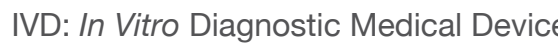
In particular, loss of TP53 is reported in 10% of patients with chronic lymphocytic leukaemia (CLL), and is considered to be the poorest prognostic marker in that disease[1,2]. In acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), TP53 loss is associated with a poor outcome and is often seen as a marker of disease progression or secondary disease. [3-5]

TP53 loss in patients with multiple myeloma is a late event, where it is seen as a marker of disease progression and is associated with a very poor prognosis[6,7].

In non-Hodgkin lymphoma, TP53 losses are reported in diffuse large B-cell lymphoma (DLBCL) often as part of 'dual-hit' lymphoma or plasmablastic phenotypes.[8] In mantle cell lymphoma (MCL), TP53 losses are associated with a poor outcome, and with a dismal outcome when seen with concurrent CDKN2A deletions.[9]

TP53 loss has also been reported in a wide range of solid tumour types including gastric cancer[9] breast cancer[10] and non-small cell lung cancer[11].





CMP-H039 v006

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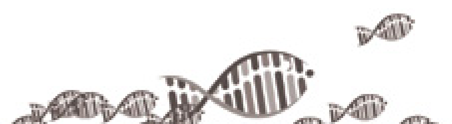
***A similar product is also available within the Haematology range, refer to page 53.**

IVD: *In Vitro* Diagnostic Medical Device



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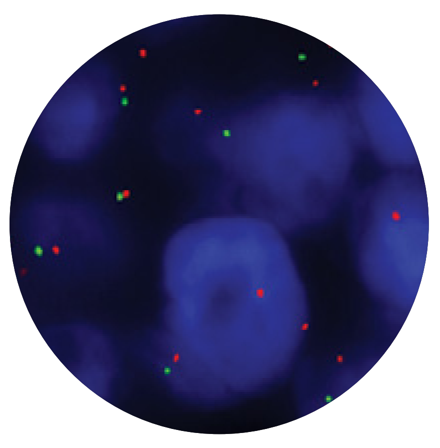
RB1 Deletion



The RB1 (*RB transcriptional corepressor 1*) gene located at 13q14.2 is a tumour suppressor gene. Mutations or losses of the RB1 gene have been shown to cause retinoblastoma, an eye cancer that is seen in infants and small children[1].

Losses or mutations of the RB1 gene are also implicated secondary tumours, such as osteosarcoma or soft tissue sarcoma[2], arising in patients with retinoblastoma.

Deletions of 13q including the RB1 gene may also occur as a result of a progressional tumourigenic event in some leukaemias[3], as well as in some breast, lung, bladder, oesophagus and prostate cancers[4].

Heterogeneous interstitial deletions of the 13q14 region are the most common cytogenetic aberrations seen in patients with chronic lymphocytic leukaemia (CLL), seen in up to 60% of cases[5]. In approximately 20% of cases, these deletions will encompass the RB1 locus; these larger deletions have been associated with a shortened survival compared with patients that have smaller deletions that do not include the RB1 locus[6].

Chromosome 13 losses and larger deletions of the long arm of chromosome 13, encompassing the RB1 locus, are reported in approximately 50% of cases of multiple myeloma[7,8].

Deletions of the long arm of chromosome 13 that include the RB1 locus have also been reported in patients with myeloid neoplasia and acute lymphoblastic leukaemia[9,10].

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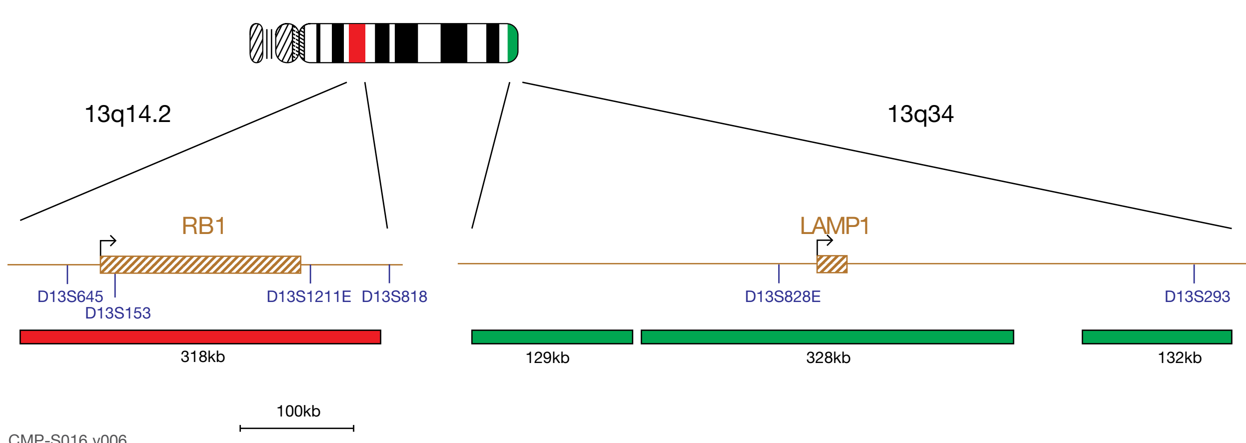

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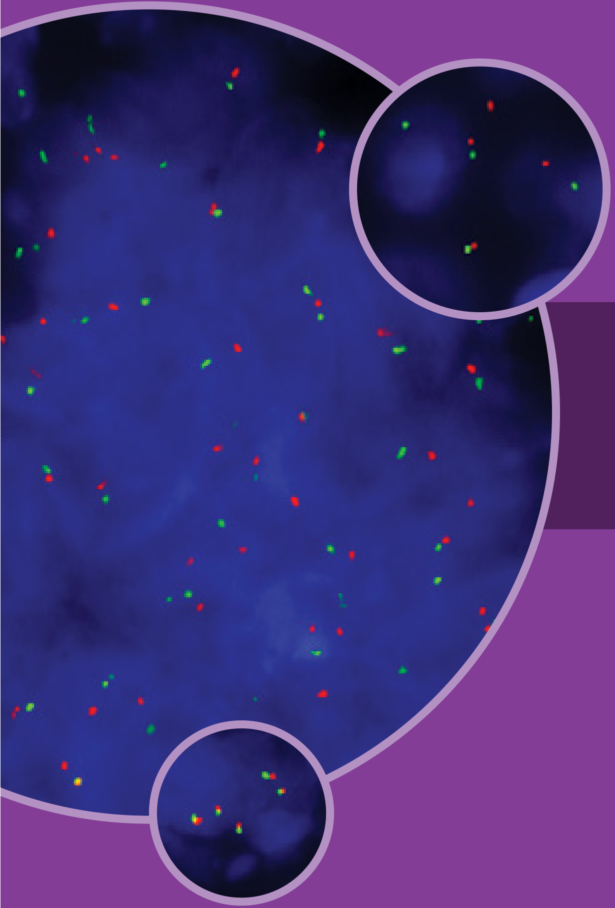
IVD: *In Vitro* Diagnostic Medical Device



Pathology

Contents

Cytocell FISH probes are CE marked IVDs* unless otherwise indicated.

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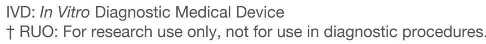
96 CHOP (DDIT3) Breakapart
97 C-MET (MET) Amplification
98 EGFR Amplification
99 EML4 Breakapart
100 EWSR1 Breakapart
101 EWSR1/ERG Translocation, Dual Fusion
102 FLI1/EWSR1 Translocation, Dual Fusion
103 FGFR1 Breakapart/Amplification
104 FOX01 Breakapart
105 FUS Breakapart
106 HER2 (ERBB2) Amplification
107 MDM2 Amplification
108 N-MYC (MYCN) Amplification
109 PAX3 Breakapart
109 PAX7 Breakapart
111 RET Breakapart
112 ROS1 Breakapart
113 ROS1 *Plus* Breakapart
114 SRD (CHD5) Deletion
115 SYT (SS18) Breakapart
116 TFE3 Breakapart † RUO
117 TMPRSS2/ERG Deletion/Breakapart
118 TOP2A Amplification/Deletion
119 ZNF217 Amplification

Pathology

The assessment of genetic changes in tissue biopsies can provide important information for prediction of tumour progression. The majority of these changes are either amplifications, deletions or other chromosomal rearrangements that can be detected using FISH.

Current methodologies, namely immunohistochemistry or blotting techniques, can provide information at the gene expression level but, when carried out on tissue sections (either cryostat or paraffin embedded), FISH can provide information at the DNA level, *in situ*, at the precise site within the tumour. This can reveal cell-to-cell heterogeneity and enable the detection of small clones of genetically distinct cells. This analysis can be made even more efficient through the use of automated image analysis systems and software.

IVD: *In Vitro* Diagnostic Medical Device
† RUO: For research use only, not for use in diagnostic procedures.



Cat. No. **LPS 100**

Tissue Pretreatment Kit

Introducing the first pretreatment kit capable of preparing slides for FISH analysis or CISH on formalin-fixed, paraffin-embedded (FFPE) tissue.

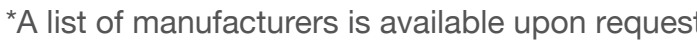
Our ready-to-use Tissue Pretreatment Kit has been optimised to produce excellent visual results with our extensive Aquarius® Pathology FISH range.

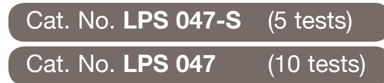
To further extend the utility of the kit we have also validated its use with other commercially available FISH (fluorescence *in situ* hybridisation) DNA probes*.

With ease-of-use and convenience in mind, our simple two stage FFPE slide preparation protocol employs the use of ready-to-use reagents, which have been optimised to increase the permeabilisation of cell membranes and facilitate penetration of the desired FISH or CISH DNA probe.

Product Information	**Kit Components**
Tissue Pretreatment Kit**	Reagent 1 (1x1L) Reagent 2 (1x10mL)

*A list of manufacturers is available upon request.
**This product is provided under an agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostics or life science use only.





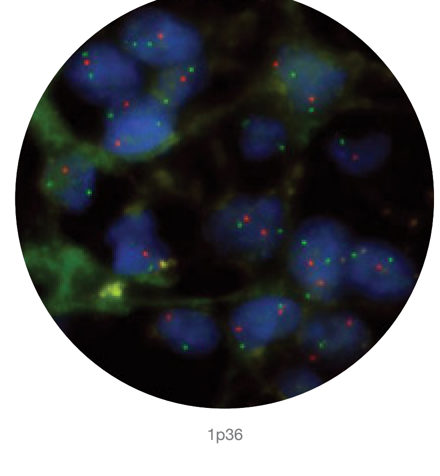
1p36/1q25 and 19q13/19p13 Deletion Probe Kit

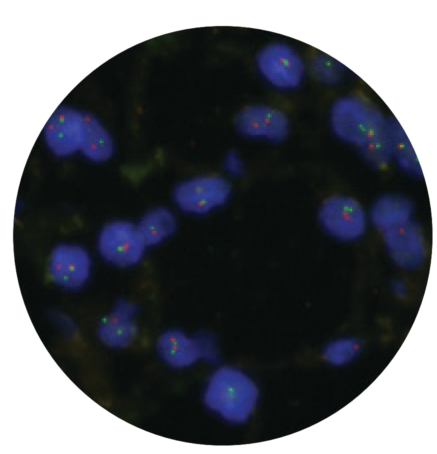
Deletions of the 1p36.32 region including the TP73 (*tumor protein p73*) gene and deletions of the 19q13.33 region including the GLTSCR1 (*BICRA, BRD4 interacting chromatin remodeling complex associated protein*) and GLTSCR2 (*NOP53, NOP53 ribosome biogenesis factor)* genes are frequently reported in cases of glial tumours.

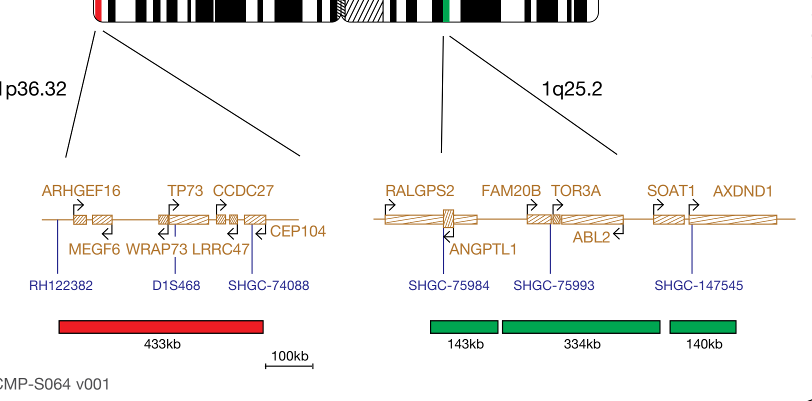
Astrocytomas and oligodendrogliomas are the most common gliomas that arise from glial cells. They make up about 40% of all CNS tumours[1] and more than 60% of primary brain cancers[2].

Concurrent losses, 'co-deletion', of the 1p36.32 and 19q13.33 regions are reported in approximately 80% of oligodendrogliomas, two-thirds of anaplastic oligodendrogliomas, as well as subsets of oligoastrocytomas and anaplastic oligoastrocytomas[3,4]; the majority of these losses have been shown to be mediated by the presence of an unbalanced t(1;19)(q10;p10) translocation. The presence of a 1p and 19q co-deletion is a strong prognostic factor in these diseases, where it is associated with improved prognosis and responsiveness to therapy[5].

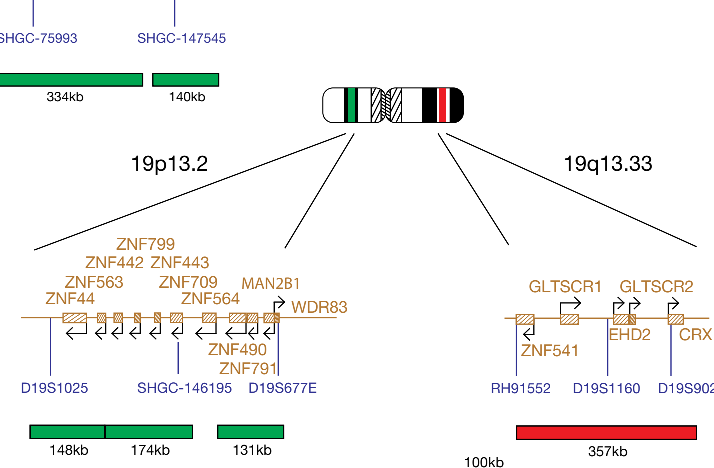
1p and 19q co-deletion has also been shown to occur in a subset of extraventricular neurocytomas, and may be associated with aggressive histology in these tumours[6].


1p36


19q13



CMP-S064 v001



CMP-S069 v001

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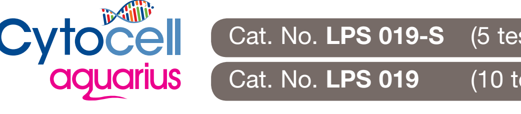
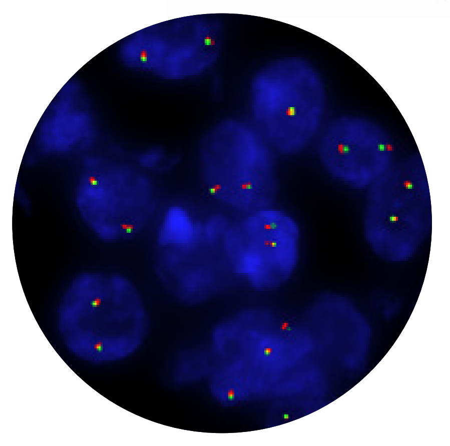
IVD: *In Vitro* Diagnostic Medical Device



ALK Breakapart



Transforming rearrangements of the ALK (*ALK receptor tyrosine kinase*) gene at 2p23 have been recognised in a subset of human haematological and solid tissue malignancies[1].

ALK fuses with NPM1 (*nucleophosmin 1*) in anaplastic lymphoma, resulting in constitutive kinase activity, which inhibits apoptosis and promotes cellular proliferation[2]. In non-small cell lung cancer (NSCLC), approximately 5% of patients will harbour ALK rearrangements, the majority as a result of an inversion involving chromosome 2, inv(2)(p21p23), causing ALK to fuse with the EML4 (*EMAP like 4*) gene[2,3]. ALK-driven tumours can be treated with crizotinib, a selective small-molecule inhibitor of ALK and its oncogenic variants[3].

ALK translocations have also been reported in a number of other malignancies including inflammatory myofibroblastic tumour[4] and renal medullary carcinoma[5]. Additionally, ALK amplification has been reported as a frequent occurrence in oesophageal cancer[6].

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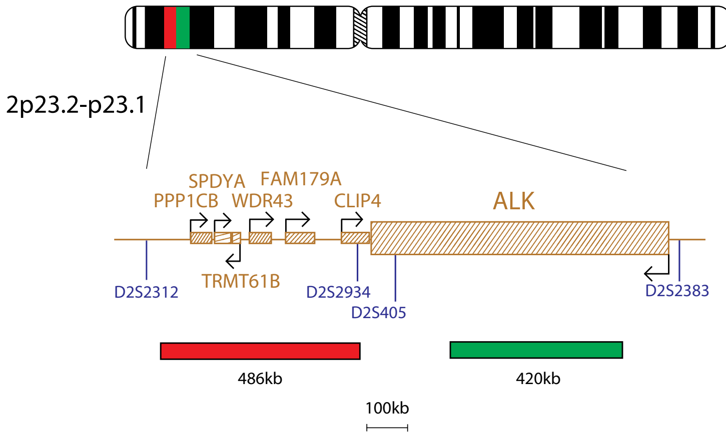

CMP-S023 v004

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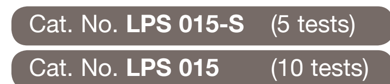
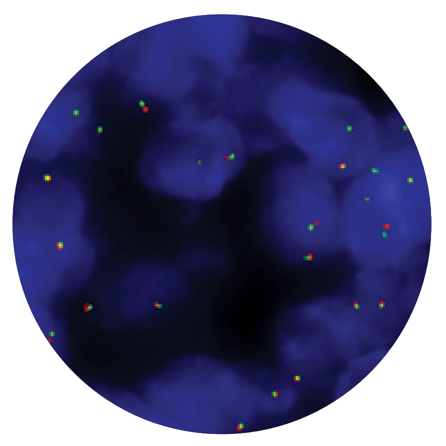


CHOP (DDIT3) Breakapart



Translocations involving the DDIT3 (*DNA damage inducible transcript 3*) gene at 12q13 are seen frequently in cases of myxoid liposarcoma.

Myxoid liposarcoma (MLS) is the most common subtype of liposarcoma[1] and is characterised by the presence of the FUS-DDIT3 t(12;16)(q13.3;p11) fusion gene. This was first described in 1986[2] and is now well-recognised and is present in at least 95% of cases of MLS3.

The transcription factor gene DDIT3 is a negative regulator of adipocyte differentiation[4]. The FUS (FUS RNA binding protein) gene is a nuclear RNA-binding protein with extensive sequence similarity to EWSR1. The FUS-DDIT3 protein interferes with adipocyte differentiation and favours proliferation over terminal differentiation.

Less commonly, a variant EWSR1-DDIT3 t(12;22)(q13;q12) translocation is seen[6].

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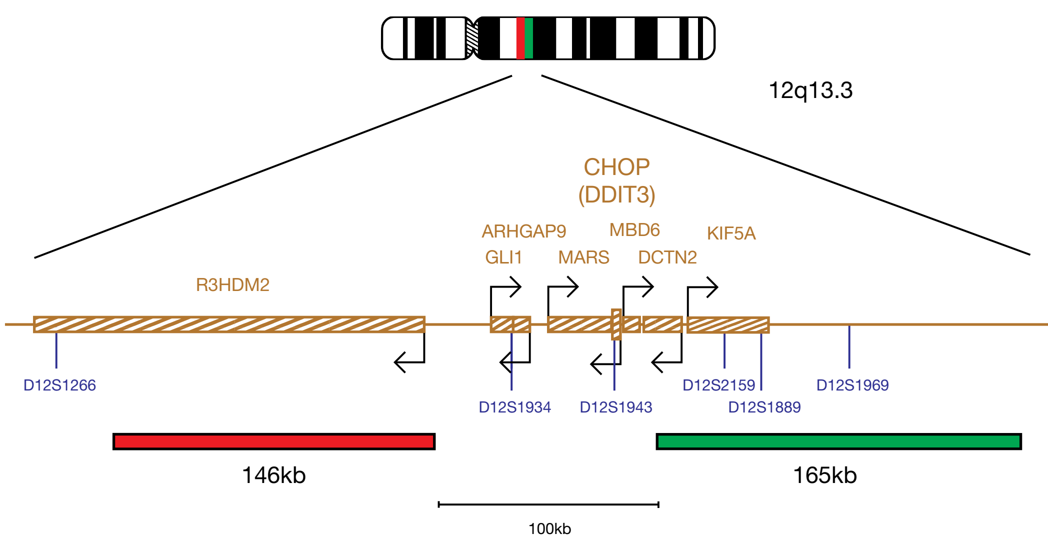

CMP-S001 v004

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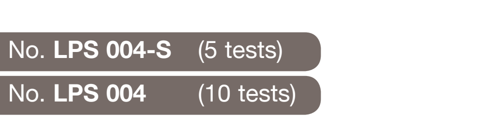
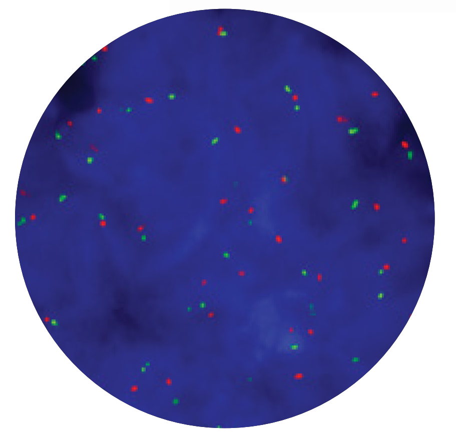


C-MET (MET) Amplification



The C-MET (*MET proto-oncogene, receptor tyrosine kinase*) gene at 7q31.2 encodes a transmembrane tyrosine kinase[1].

The MET gene regulates both cell motility and cell growth[2]; therefore, normal MET protein expression allows stem cells and progenitor cells to grow invasively. This invasive growth is required, in embryos to generate new tissues and in adults to repair wounds or regenerate tissue, such as the liver[3].

The MET gene has been shown to be overexpressed in many tumours including ovarian[4], breast[5], lung[6], thyroid[7], stomach[8], pancreatic,[9,10] and colon[11,12]. This overexpression correlates with a poor prognosis[4,13,14]. In breast cancers, MET was only shown to be co-expressed with ERBB2 in 50% of patients, indicating that it has a significant impact on tumour aggressiveness independently of ERBB2[14]. In recurrent/metastatic gastric cancer, MET gene amplification has been shown to be significantly associated with an unfavourable clinical outcome[15].

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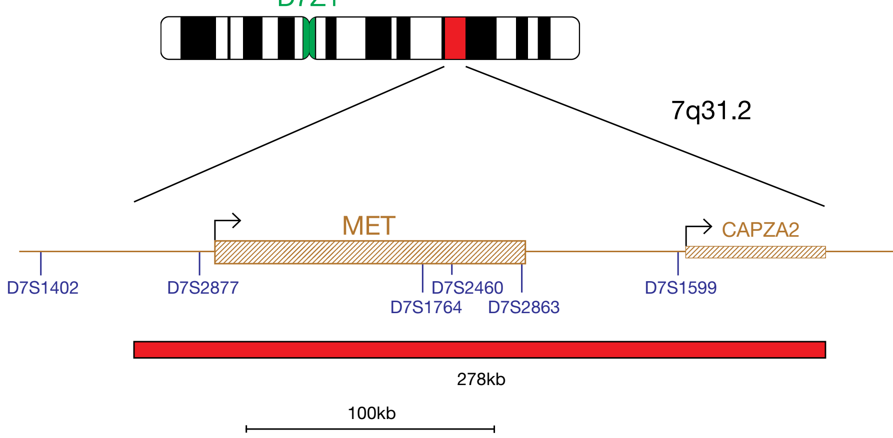

CMP-S002 v003

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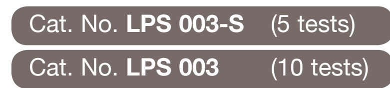
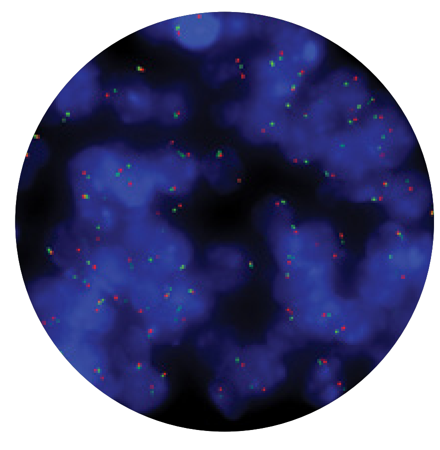


EGFR Amplification



The EGFR (*epidermal growth factor receptor*) gene at 7p11.2, encodes a type 1 tyrosine kinase receptor for members of the epidermal growth factor family. Binding of the epidermal growth factor receptor and epidermal growth factor proteins lead to signal transduction cascades and regulate signaling pathways to control cellular proliferation[1].

Abnormally-elevated EGFR kinase activity can lead to proliferative diseases such as non-small-cell lung carcinoma (NSCLC), which accounts for 80-85% of all lung cancers[2], and less frequently breast cancer[3], amongst others.

There are a number of EGFR-inhibitor drugs in clinical use, for example: gefitinib and erlotinib in NSCLC, lapatinib in breast cancer or cetuximab in colorectal cancer[4,5]. Approximately 10% of lung cancer patients show a rapid and dramatic response to these tyrosine kinase inhibitors (TKIs)[6,7].

FISH has been shown to be useful for determining the amplification status of EGFR in NSCLC, aiding the selection of patients for treatment with EGFR TKIs[8].

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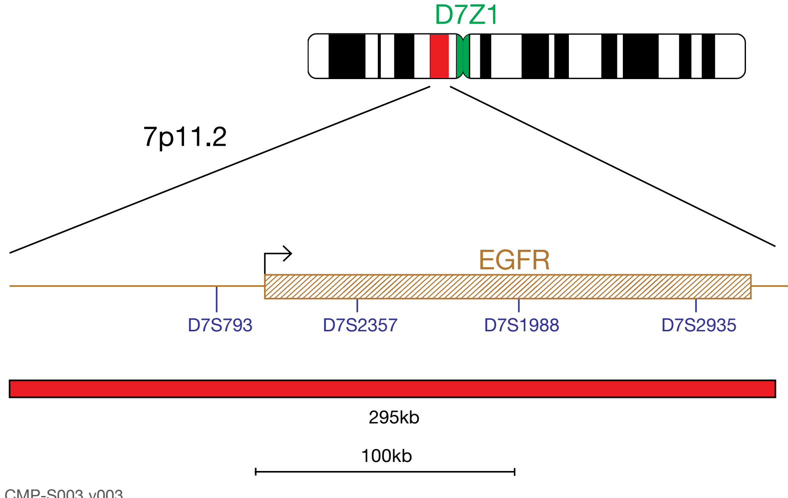
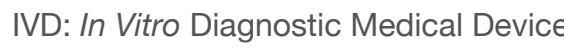
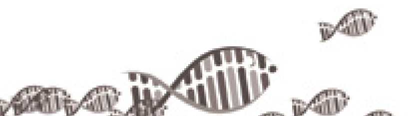


CMP-S003 v003


IVD: *In Vitro* Diagnostic Medical Device



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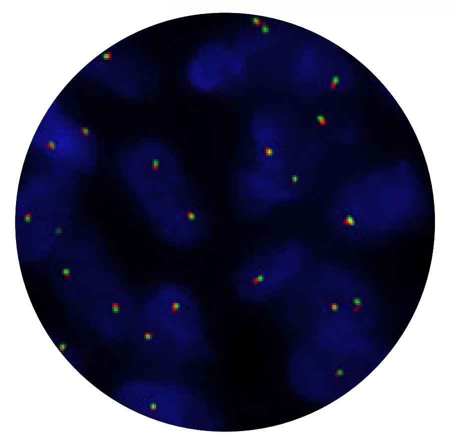
Cat. No. **LPS 020**	(10 tests)

Pathology

EML4 Breakapart



The protein encoded by the EML4 (*EMAP like 4*) gene at 2p21 is involved in microtubule formation and stabilisation[1].

A novel gene fusion of EML4 and ALK (*ALK receptor tyrosine kinase*) has been identified in patients with non-small cell lung cancer (NSCLC). The EML4-ALK fusion results from an inversion within chromosome 2p, inv(2)(p21p23), and is detected in approximately 5% of NSCLC cases[2,3,4]. ALK-driven tumours can be treated with crizotinib, a selective small-molecule inhibitor of ALK and its oncogenic variants[5].

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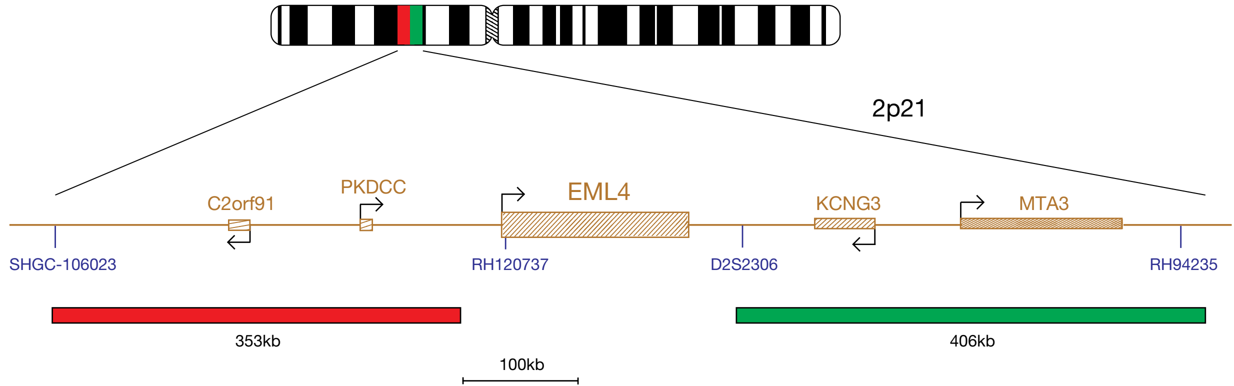
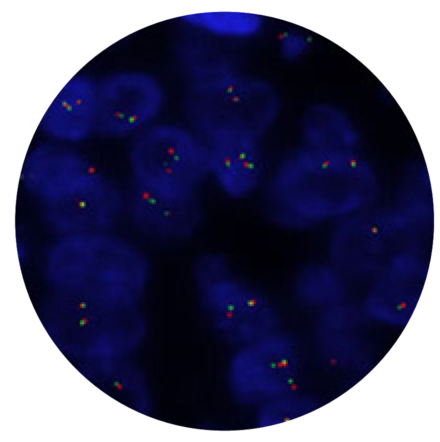


CMP-S024 v003

IVD: *In Vitro* Diagnostic Medical Device

EWSR1 Breakapart



Rearrangements involving the EWSR1 (*EWS RNA binding protein 1*) gene at 22q12.2 are seen in a wide variety of mesenchymal lesions, and involve a large number of recognised partner genes.

Ewing sarcoma is the second most frequent primary bone cancer in patients under 20 years of age[1]. Approximately 85% of Ewing sarcomas are characterized by a t(11;22)(q24.3;q12.2) translocation involving EWSR1 and FLI1[2]. Approximately 10% of the remaining cases have a variant t(21;22)(q22;q12.2) translocation involving EWSR1 and ERG[3]. The remaining cases involve one of the many other EWSR1 translocation partners such as 7p21 (ETV1), 17q21.3 (ETV4) or 2q35 (FEV) translocations with EWSR1[4].

Recurrent EWSR1 rearrangements are also recognised in a number of other conditions, including: translocations with WT1 via the t(11;22)(p13;q12.2) in desmoplastic small round cell tumours[5,6]; translocations with DDIT3 via the variant t(12;22)(q13.3;q12.2) in myxoid liposarcoma[7] and t(9;22)(q22;q12.2) translocations in extraskeletal myxoid chondrosarcoma, which fuse the EWSR1 gene with the NR4A3 gene[8].

The EWSR1 breakapart probe can also be used to distinguish clear cell sarcoma from melanoma, a distinction that is difficult to make via either histology or immunohistology. The EWS-ATF1 translocation, t(12;22)(q13;q12), has been identified in more than 90% of clear cell sarcoma, yet has not been observed in melanoma[9,10].

This breakapart probe has been designed to allow detection of EWSR1 rearrangements regardless of the partner gene.

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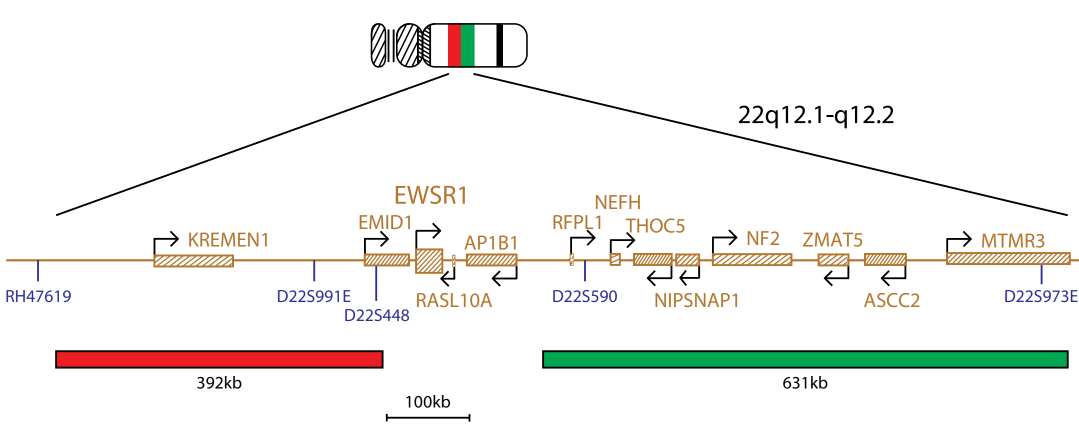

CMP-S004 v004

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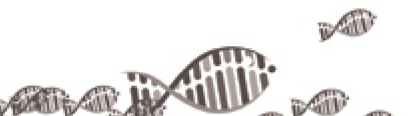

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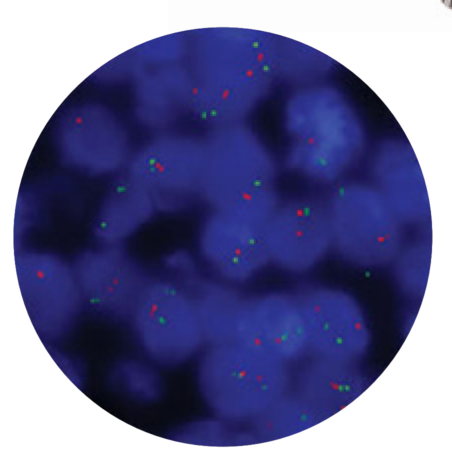
EWSR1/ERG Translocation, Dual Fusion



Ewing sarcoma is the second most frequent primary bone cancer in patients under 20 years of age[1].

Approximately 10% of Ewing sarcomas will have a t(21;22) (q22;q12.2) translocation involving EWSR1 and ERG (*ETS transcription factor ERG*)[2]. The majority of cases, up to 85%, of Ewing sarcoma will show a t(11;22)(q24.3;q12.2) translocation involving the EWSR1 and FLI1 genes[3]. The remaining cases involve one of the many other EWSR1 translocation partners such as 7p21 (ETV1), 17q21.3 (ETV4) or 2q35 (FEV) translocations with EWSR1[4].

REFERENCES

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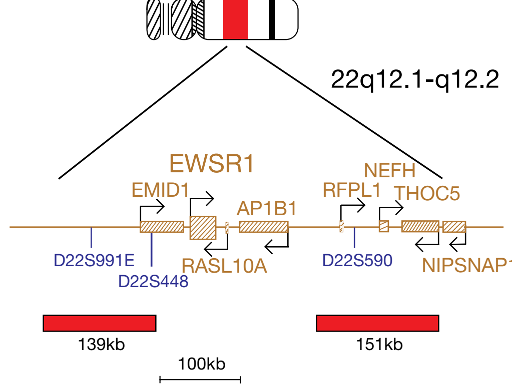
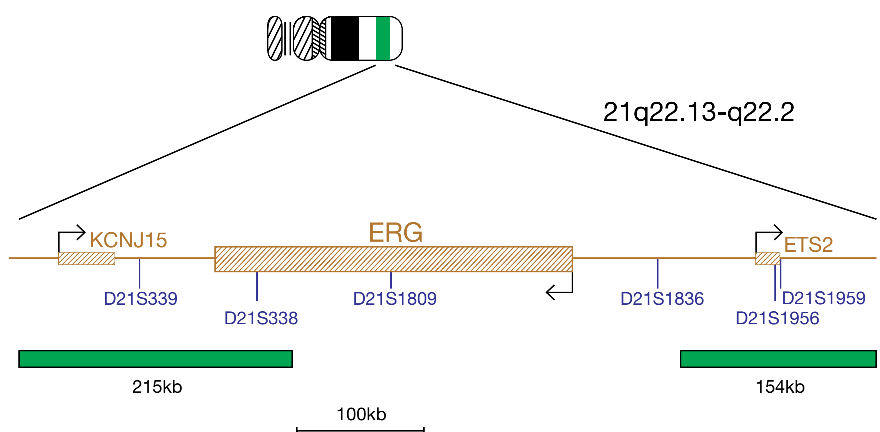
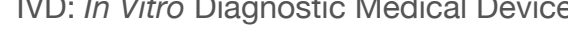
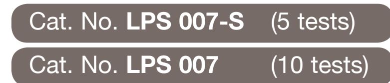


CMP-S005 v003

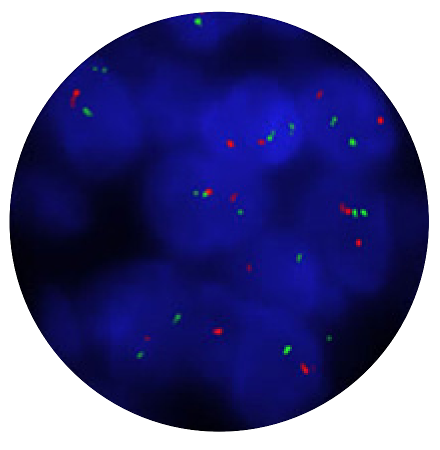


CMP-S006 v003


IVD: *In Vitro* Diagnostic Medical Device



FLI1/EWSR1 Translocation, Dual Fusion



Ewing sarcoma is the second most frequent primary bone cancer in patients under 20 years of age[1].

Approximately 85% of Ewing sarcomas are characterised by a t(11;22)(q24.3;q12.2) translocation involving the EWSR1 and FLI1 (*Fli-1 proto-oncogene, ETS transcription factor*) genes[2]. Approximately 10% of the remaining cases have a variant t(21;22)(q22;q12.2) translocation involving EWSR1 and ERG[3]. The remaining cases involve one of the many other EWSR1 translocation partners such as 7p21 (ETV1), 17q21.3 (ETV4) or 2q35 (FEV) translocations with EWSR1[4].

REFERENCES

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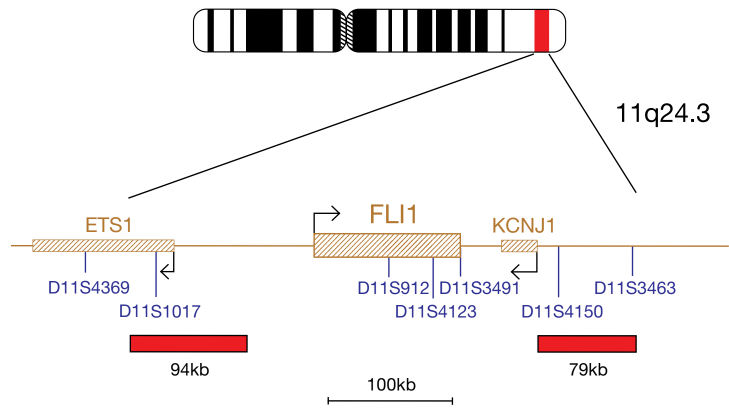
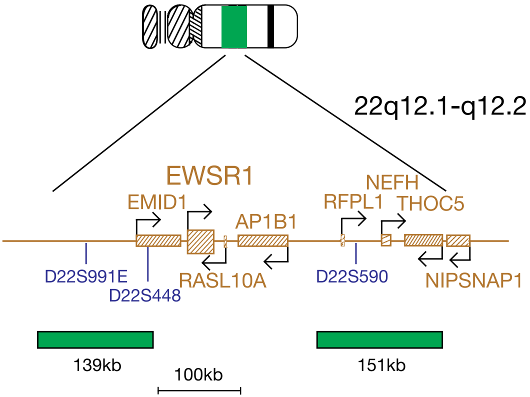


CMP-S007 v003



CMP-S008 v003

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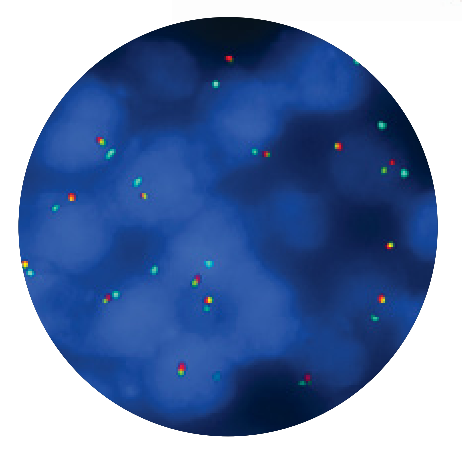
FGFR1 Breakapart/Amplification



The FGFR1 (*fibroblast growth factor receptor 1*) gene, at 8p11.2, has been shown to be amplified in approximately 10% of breast cancers[1,2], in approximately 20% of squamous cell carcinomas of the lung (SCCL)[3] and in approximately 9% of non-small-cell lung cancers (NSCLC)[4]. The FGFR1 gene is also involved in translocations in patients with 8p11 myeloproliferative syndrome[5].

Amplification of FGFR1 has been shown to be associated with a poor outcome in breast cancer, as over-expression of the gene product has been implicated in early relapse[6]. Amplification of FGFR1 has also been associated with a poor prognosis in both squamous cell carcinoma of the lung (SCCL) and non-small-cell lung cancer (NSCLC)[7,8].

FGFR1 is a receptor tyrosine kinase for fibroblast growth factors[9]. FGFR1 rearrangements are associated with 8p11 myeloproliferative syndrome (EMS)/stem cell leukaemia-lymphoma syndrome. A number of gene fusions that have constitutive tyrosine kinase activity have been described in EMS, including: FGFR1-ZNF198 (ZMYM2), the most common, via a t(8;13)(p11;q12) translocation; FGFR1-CEP110 (CNTRL) via a t(8;9)(p11;q33) translocation, FGFR1-FOP (FGFR10P) via a t(6;8)(q27;p11) translocation and FGFR1-BCR via a t(8;22)(p11;q22) translocation[10,11].

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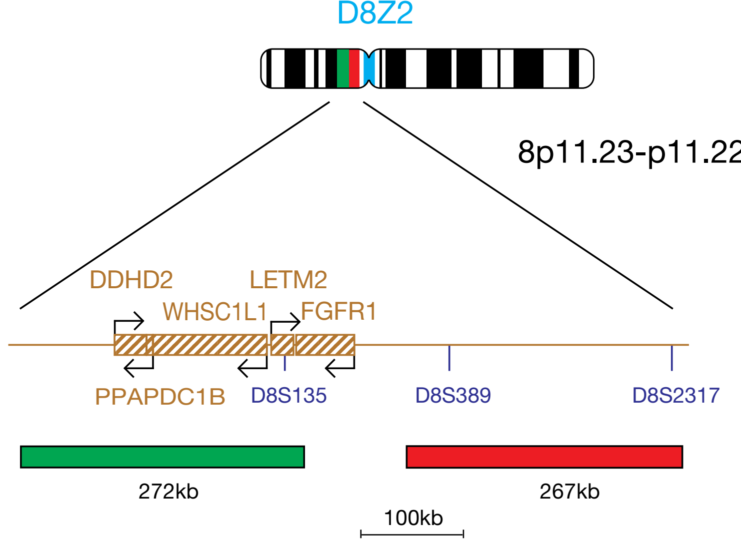
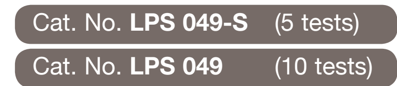
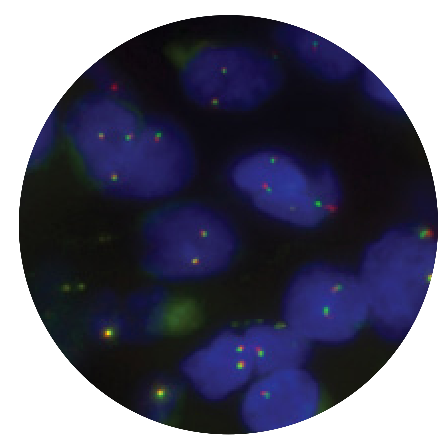


CMP-S009 v004

IVD: *In Vitro* Diagnostic Medical Device



FOXO1 Breakapart



Translocations involving the FOXO1 (*forkhead box O1*) gene at 13q14.1 and either the PAX3 (*paired box 3*) gene at 2q36.1 or the PAX7 (*paired box 7*) gene at 1p36.1 are seen frequently in cases of alveolar rhabdomyosarcoma[1,2].

Rhabdomyosarcoma is the most common soft-tissue sarcoma seen in children and younger adults with two major histological subtypes: alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS)[3]. FOXO1 rearrangements are recognised recurrent abnormalities seen in ARMS, but not seen in ERMS[1,2].

Approximately 55% of cases of ARMS are associated with a PAX3-FOXO1 rearrangement via a t(2;13)(q36.1;q14) translocation and 22% of cases of ARMS are associated with a PAX7- FOXO1 rearrangement via a t(1;13)(p36;q14) translocation[4]. These translocations lead to the fusion of transcription factor FOXO1 to the transcription factors PAX3 and PAX7 located at 2q36.1 and 1p36.1 respectively[2].

Studies have shown that ARMS patients with PAX-FOXO1 rearrangements have an inferior outcome compared to ERMS patients, whereas ARMS patients without PAX-FOXO1 rearrangements show similar outcomes to ERMS[2,5].

A subset of patients with ARMS may show fusion gene amplification. This is most commonly associated with the presence of PAX7-FOXO1 rearrangements and has been shown to be associated with significantly improved outcome over ARMS patients with PAX-FOXO1 rearrangements without fusion gene amplification[6].

This breakapart probe design allows the detection of FOXO1 rearrangements, regardless of the partner gene involved.

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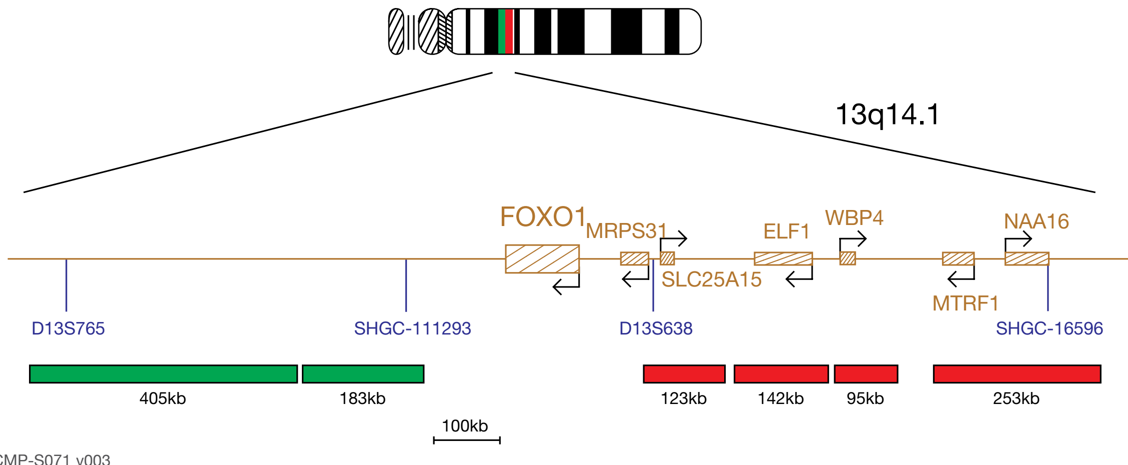


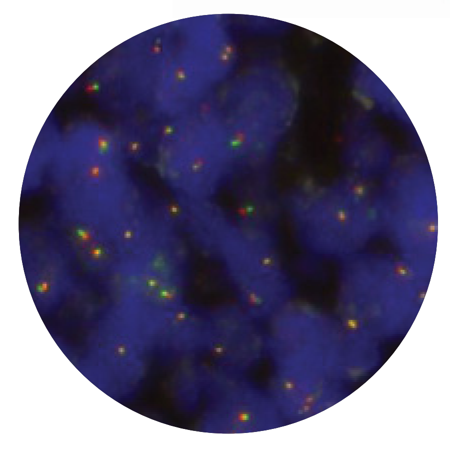
CMP-S071 v003

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPS 050-S** (5 tests)

Cat. No. **LPS 050** (10 tests)

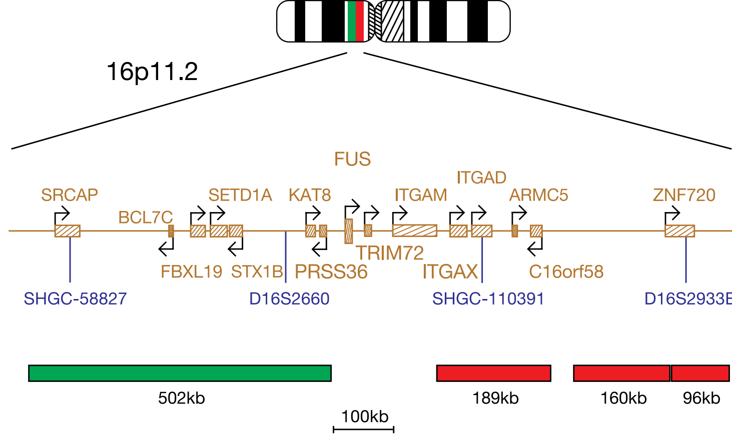
FUS Breakapart Probe



The FUS (*FUS RNA binding protein*) gene at 16p11.2 is a member of the FET family of protein-encoding genes, closely-related to the EWSR1 (*EWS RNA binding protein 1*) gene[1].

Recurrent rearrangements involving the FUS gene with a number of different partner genes have been reported in various types of neoplastic disease, notably soft tissue sarcomas and acute myeloid leukaemia. In some tumour types FUS and EWSR1 may replace each other as fusion partners[2].

In soft tissue sarcoma, approximately 90% of cases of myxoid liposarcoma are characterised by the presence of a FUS-DDIT3 rearrangement arising from a t(12;16)(q13;p11) translocation[3,4]; the FUS-CREB3L1 and the FUS-CREB3L2 fusions, resulting from t(11;16)(p11;p11) and t(7;16)(q32-34;p11) translocations respectively are characteristic of low-grade fibromyxoid sarcoma[5], whereas the t(12;16)(q13;p11) translocation resulting in a FUS-ATF1 fusion gene is seen in angiomatoid fibrous histiocytoma[6]. This breakapart probe has been designed to allow detection of FUS rearrangements regardless of the partner gene involved.



CMP-S072 v002

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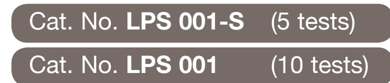
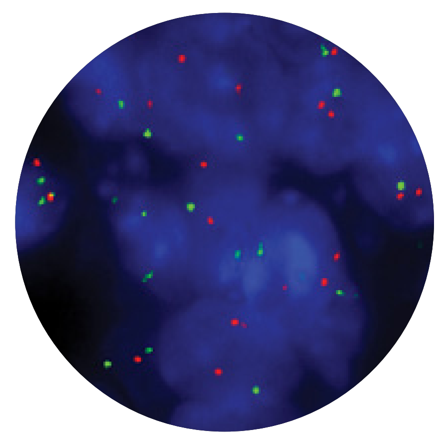
IVD: *In Vitro* Diagnostic Medical Device



HER2 (ERBB2) Amplification



The ERBB2 (*erb-b2 receptor tyrosine kinase 2*) gene, located at 17q12, is a member of the epidermal growth factor (EGF) receptor family[1].

ERBB2 amplification is seen in approximately 15% of breast cancers[2] and, in the absence of therapy, is associated with a poor prognosis for the patient[3]. Treatment of patients with ERBB2 amplification using the monoclonal antibody trastuzumab has been shown to be effective in the treatment of breast cancer, increasing overall survival time by suppressing ERBB2 activity and leading to cell death[4,5].

Similar results have been obtained for a variety of other malignant neoplasms overexpressing ERBB2, including some ovarian[6], stomach[7,8], salivary gland[9] and lung cancers[10].

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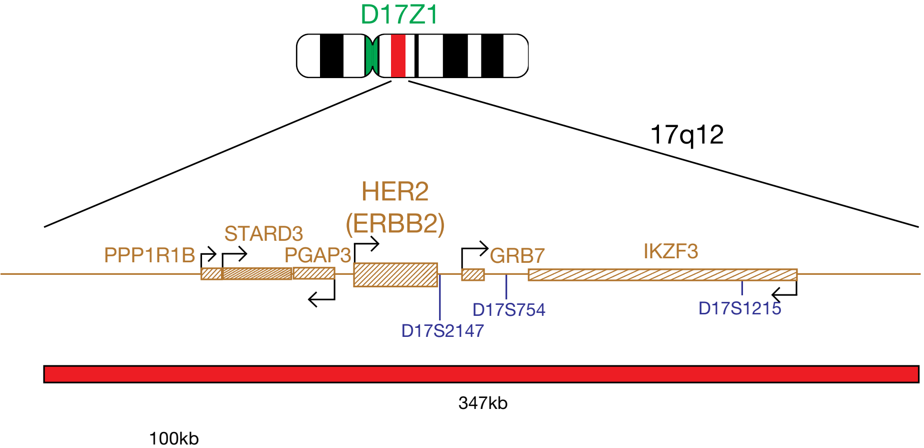
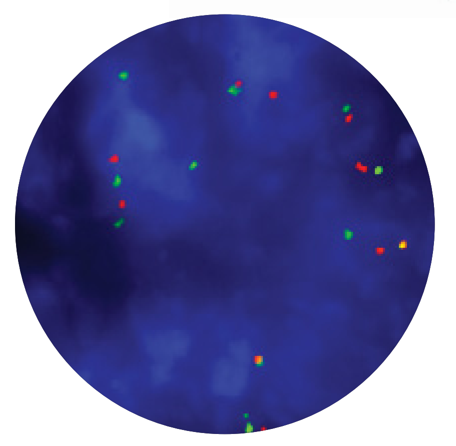


CMP-S010 v002

IVD: *In Vitro* Diagnostic Medical Device

MDM2 Amplification



The MDM2 (*MDM2 proto-oncogene*) gene at 12q15, when overexpressed, enhances the tumourigenic potential of cells. MDM2 overexpression is seen in many cancer types with an overall frequency of gene amplification of around 7%[1,2].

MDM2 protein overexpression often results from MDM2 gene amplification, which has been reported in well-differentiated liposarcoma, osteosarcoma, colorectal cancer, non-small cell lung cancer and glioma, amongst many others, with the prognostic implications of the presence of MDM2 amplification varying with the tumour type[2,3,4,5,6].

The MDM2 oncogene product forms a tight complex with the p53 tumour suppressor protein that inhibits p53-mediated transactivation, leading to escape from p53 regulated growth control[7]. A number of small-molecule inhibitors that block the MDM2-p53 interaction, thereby reactivating p53 function, have advanced into human cancer clinical trials[8,9].

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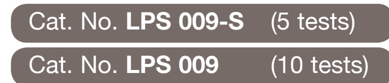
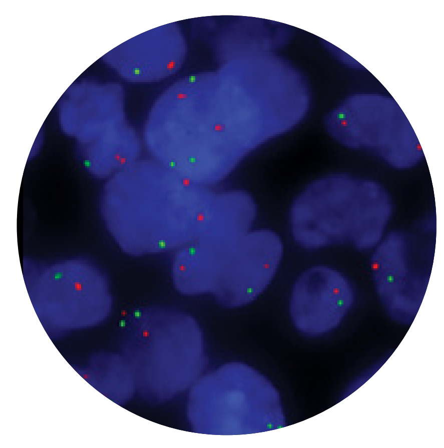
D12Z1
12q15
MDM2
NUP107
CPM
D12S1501
146kb
100kb

CMP-S012 v003

IVD: *In Vitro* Diagnostic Medical Device



N-MYC (MYCN) Amplification



The proto-oncogene MYCN (*MYCN proto-oncogene, bHLH transcription factor*) located at 2p24.3, is a transcription factor that plays a role in regulation of cell growth and proliferation.

MYCN mainly expressed in the developing nervous system and is critical during neural crest embryogenesis; it then becomes rapidly down-regulated as tissues become terminally differentiated and growth-arrested[1]. Over-expression of MYCN appears to block differentiation and increase cell proliferation[2].

In neuroblastoma, the most common extracranial solid tumour in childhood, MYCN gene amplification is seen in 16% to 25% of tumours and is associated with a poor clinical outcome[3,4].

In medulloblastoma, the most common malignant brain tumour in childhood, MYCN gene amplification is seen mainly within SHH and Group 4 medulloblastomas and is associated with a less favourable outcome[5,6]

Amplification of the MYCN gene has also been reported in other cancers including a subset of unilateral retinoblastoma tumours in the absence of detectable RB1 mutations[7].

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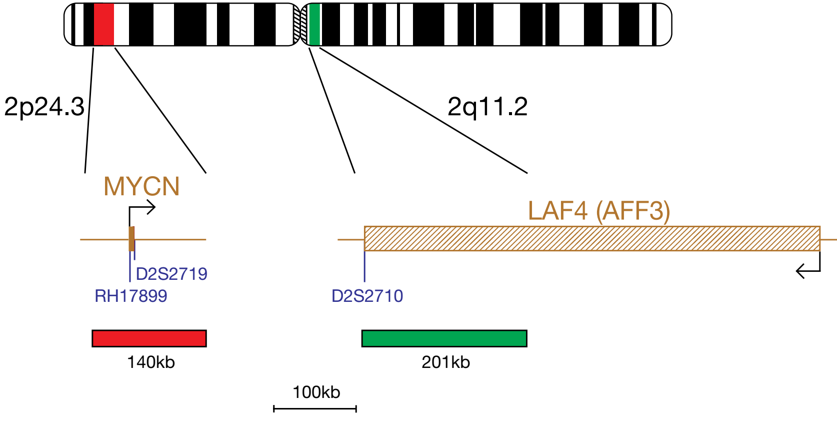
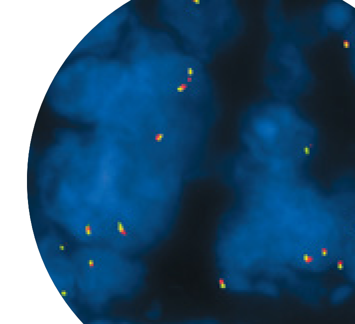


CMP-S013 v004

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPS 012-S** (5 tests) Cat. No. **LPS 013-S** (5 tests)
Cat. No. **LPS 012** (10 tests) Cat. No. **LPS 013** (10 tests)

PAX3 Breakapart and PAX7 Breakapart



PAX7 Breakapart

Translocations involving the FOXO1 (*forkhead box O1*) gene at 13q14 and either the PAX3 (*paired box 3*) gene at 2q36.1 or the PAX7 (*paired box 7*) gene at 1p36.13 are seen frequently in cases of alveolar rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue sarcoma seen in children and younger adults with two major histological subtypes: alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS). FOXO1 rearrangements are recognised recurrent abnormalities seen in ARMS, but not seen in ERMS,[1,2].

Approximately 55% of cases of ARMS are associated with a PAX3-FOXO1 rearrangement via a t(2;13)(q36.1;q14) translocation and 22% of cases of ARMS are associated with a PAX7-FOXO1 rearrangement via a t(1;13)(p36;q14) translocation[3]. These translocations lead to the fusion of transcription factor FOXO1 to the transcription factors PAX3 and PAX7 located at 2q36.1 and 1p36.13 respectively[2].

Studies have shown that ARMS patients with PAX-FOXO1 rearrangements have an inferior outcome compared to ERMS patients, whereas ARMS patients without PAX-FOXO1 rearrangements show similar outcomes to ERMS[2,4].

A subset of patients with ARMS may show fusion gene amplification. This is most commonly associated with the presence of PAX7-FOXO1 rearrangements and has been shown to be associated with significantly improved outcome over ARMS patients with PAX-FOXO1 re-arrangements without fusion gene amplification[5].

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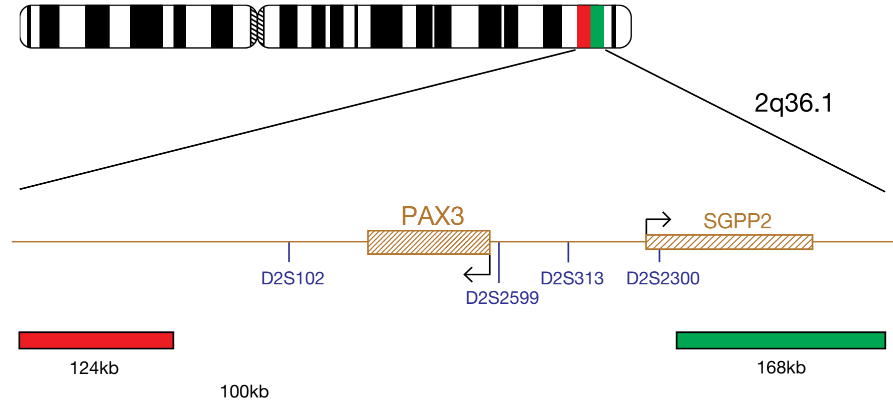
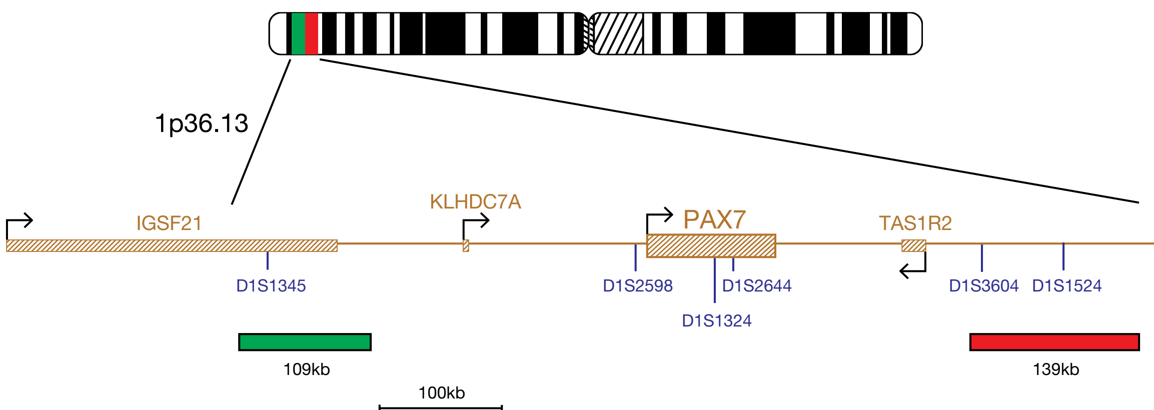
IVD: *In Vitro* Diagnostic Medical Device

PAX3 Cat. No. LPS 012



CMP-S014 v003

PAX7 Cat. No. LPS 013

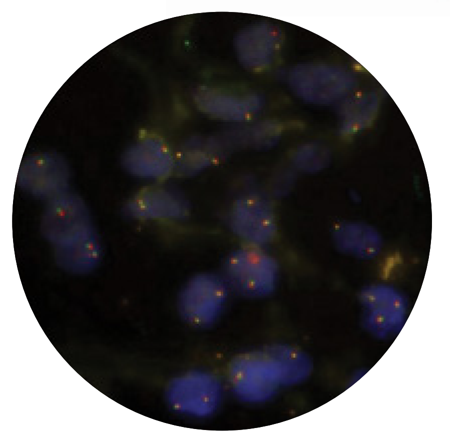


CMP-S015 v004

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPS 045-S** (5 tests)
Cat. No. **LPS 045** (10 tests)

RET Breakapart



The RET (*ret proto-oncogene*) gene at 10q11 encodes for a transmembrane tyrosine kinase receptor involved in the control of cell differentiation, cell proliferation, and cell survival[1].

Rearrangements involving the RET gene are recognised recurrent abnormalities seen in 1-2% patients with lung adenocarcinomas, where it is seen fused with KIF5B[2,3], and papillary thyroid carcinoma where it is seen fused to a number of different partner genes including: CCDC6, PRKAR1A and NCOA4[4,5]. The features of the proteins encoded by all types of RET fusion gene are similar to those of ALK: coiled-coil domains in the N-terminal fusion partners cause the RET domains to dimerize, resulting in activation of RET tyrosine kinase in the absence of ligands[3].

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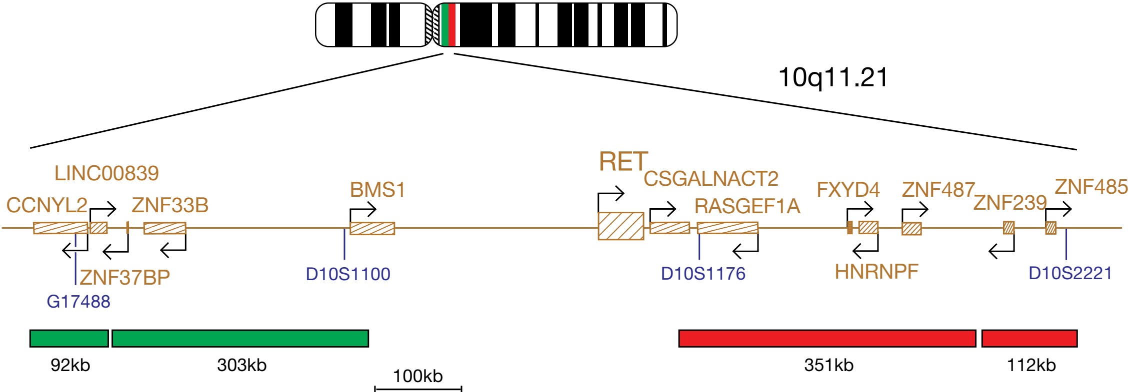
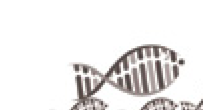
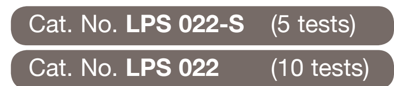


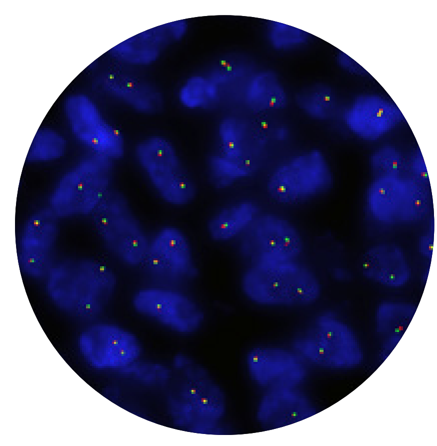
CMP-S055 v002

IVD: *In Vitro* Diagnostic Medical Device





ROS1 Breakapart



The ROS1 (*ROS proto-oncogene 1, receptor tyrosine kinase*) gene at 6q22.1 is an ALK (*ALK receptor tyrosine kinase*) gene paralogue which encodes a type I integral membrane protein with tyrosine kinase activity[1].

ROS1 rearrangements define a molecular subset of non-small cell lung cancer (NSCLC) and are seen in approximately 2% of patients with NSCLC[2]. A number of partner genes have been identified, including SLC34A2, CD74 and SDC4[3]. It has been shown that these ROS1 fusions activate the pSTAT3, PI3K/AKT/mTOR and SHP-2 phosphatase pathways[4,5].

NSCLC patients with ROS1 rearrangements have been shown to respond to treatment with ALK/MET tyrosine kinase inhibitors, such as crizotinib[6].

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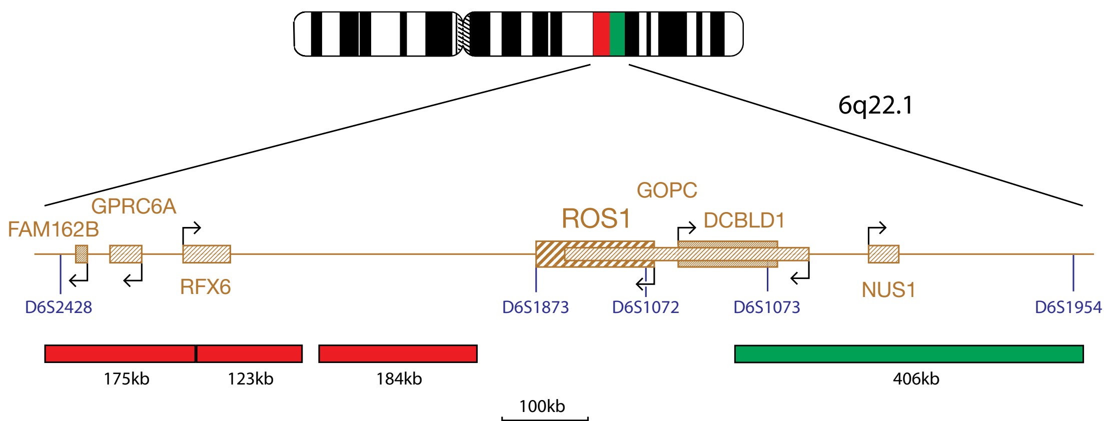
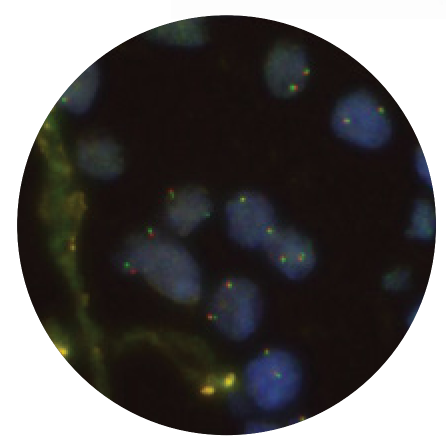


CMP-S045 v003

IVD: *In Vitro* Diagnostic Medical Device

ROS1 *Plus* Breakapart



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ROS1 rearrangements define a molecular subset of non-small cell lung cancer (NSCLC) and are seen in approximately 2% of patients with NSCLC[2]. A number of partner genes have been identified, including SLC34A2, CD74 and SDC4[3]. It has been shown that these ROS1 fusions activate the pSTAT3, PI3K/AKT/mTOR and SHP-2 phosphatase pathways[4,5].

NSCLC patients with ROS1 rearrangements have been shown to respond to treatment with ALK/MET tyrosine kinase inhibitors, such as crizotinib[6].

ROS1 rearrangements with the GOPC (*golgi associated PDZ and coiled-coil motif containing*) gene fusion partner were originally reported in glioblastoma, but have now also been detected on cholangiocarcinoma, ovarian cancer and NSCLC patient samples[7-9].

The ROS1 *Plus* design covers the ROS1 region and the region deleted in ROS1-GOPC fusions.

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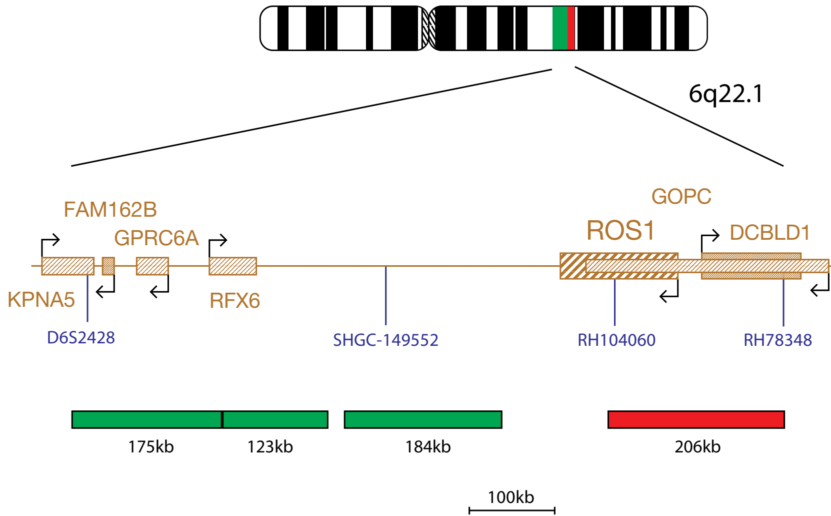
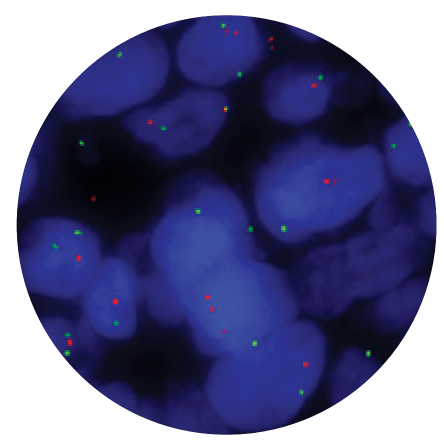


CMP-S060 v003

SRD (CHD5) Deletion



Deletions of the 1p36 region, including the CHD5 (*chromodomain helicase DNA binding protein 5*) gene are seen in a number of human cancers[1].

The CHD5 gene acts as a tumour suppressor, and has been shown to be commonly deleted in neuroblastomas[2]. Deletion of the short arm of chromosome 1 is one of the most characteristic genetic changes in neuroblastoma, the most common tumour of infants, which accounts for around 8-10% of childhood cancers and 15% of childhood cancer deaths[3]. The CHD5 gene has been characterised as the lead tumour suppressor candidate from the 1p36 smallest region of consistent deletion (SRD) region in neuroblastoma[4].

Deletions of this gene have also been reported in gliomas as well as breast, lung, ovarian, gastric, laryngeal, gallbladder, prostate and colorectal cancers[3].

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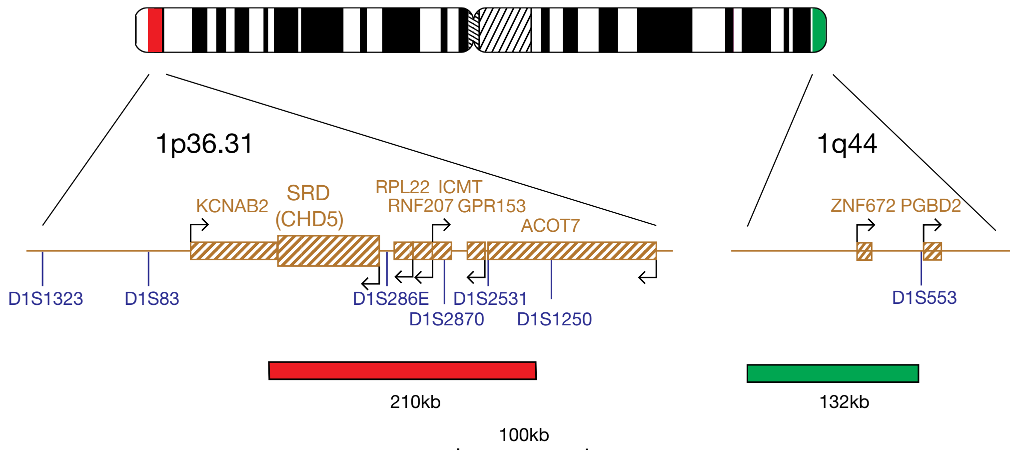
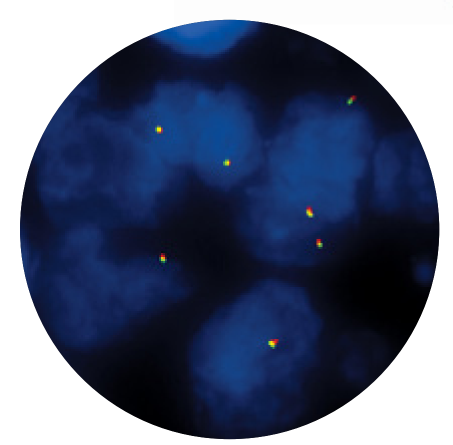


CMP-S017 v004

IVD: *In Vitro* Diagnostic Medical Device

SYT (SS18) Breakapart



Rearrangements involving the SS18 (*SS18 subunit of BAF chromatin remodeling complex*) gene located at 18q11.2 are seen in more than 90% of synovial sarcomas[1].

Synovial sarcomas account for up to 10% of soft-tissue sarcomas, typically arising in the para-articular regions in adolescents and young adults[2]. The tumour is characterised by the presence of a t(X;18)(p11;q11.2) translocation[3,4].

The translocation fuses the SS18 gene to either one of two highly homologous genes at Xp11: SSX1 (*SSX family member 1*) or SSX2 (*SSX family member 2*) . In less than 1% of cases, SS18 will be fused to a third gene, SSX4[5].

SYT-SSX1 and SYT-SSX2 are thought to disrupt transcription and the subsequent expression of specific target genes[6,7].

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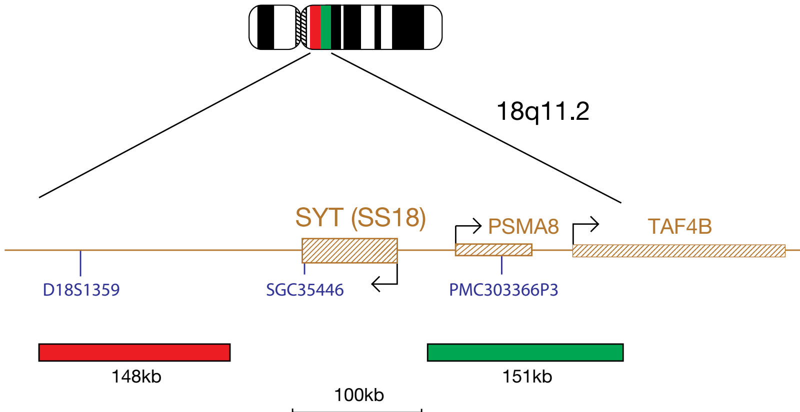
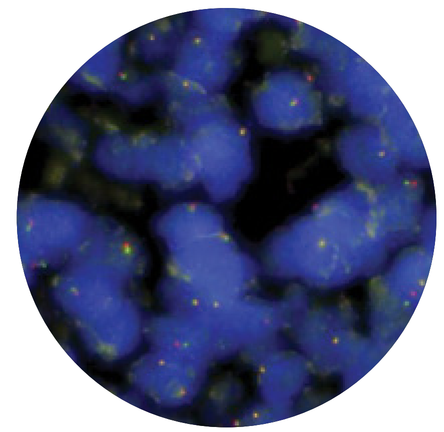


CMP-S018 v003

IVD: *In Vitro* Diagnostic Medical Device

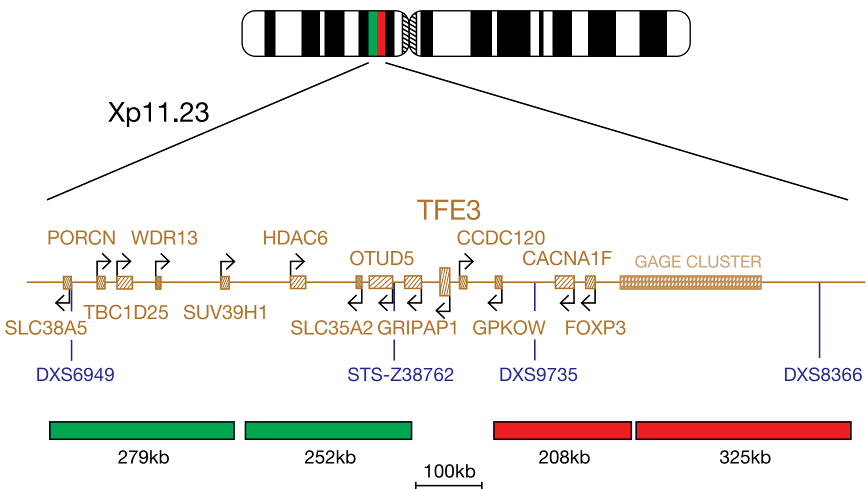
Cat. No. **RU-LPS 051-S** (50ul)
Cat. No. **RU-LPS 051** (100ul)

TFE3 Breakapart†



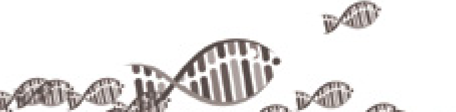
For research use only **RUO**

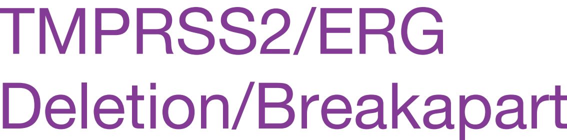
The TFE3 Breakapart probe consists of two probes (279kb and 252kb), labelled in green, situated distal to the TFE3 gene and covering markers DXS6949 and STS-Z38762 and two probes (208kb and 325kb), labelled in red, situated proximal to the TFE3 gene and covering markers DXS9735 and DXS8366.

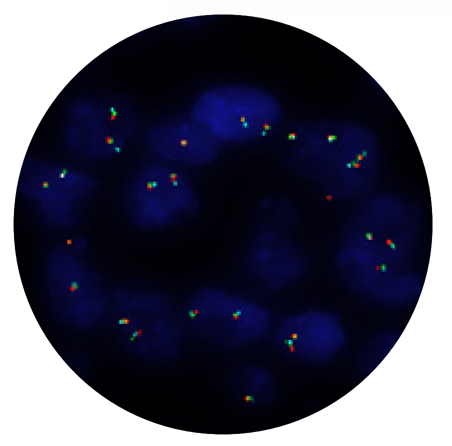


CMP-S073 v001

† For research use only, not for use in diagnostic procedures.







The TMPRSS2 (*transmembrane serine protease 2*) and ERG (*ETS transcription factor ERG*) genes are located at 21q22.

Approximately 50% of prostate tumours show an intrachromosomal deletion of 3Mb on chromosome 21 that fuses the TMPRSS2 gene to the ERG gene[1]. This rearrangement places ERG, a member of the ETS (*erythroblast transformation-specific*) family of transcription factors, under the androgen-regulated transcriptional control of TMPRSS[2]. In approximately 2-8% of prostate cancers the TMPRSS2 gene is fused with a different partner gene from the ETS family, for example ETV1, ETV4 or ETV5[3]. The presence of a TMPRSS2-ETS fusion has been associated with an aggressive disease phenotype in prostate cancer[4].

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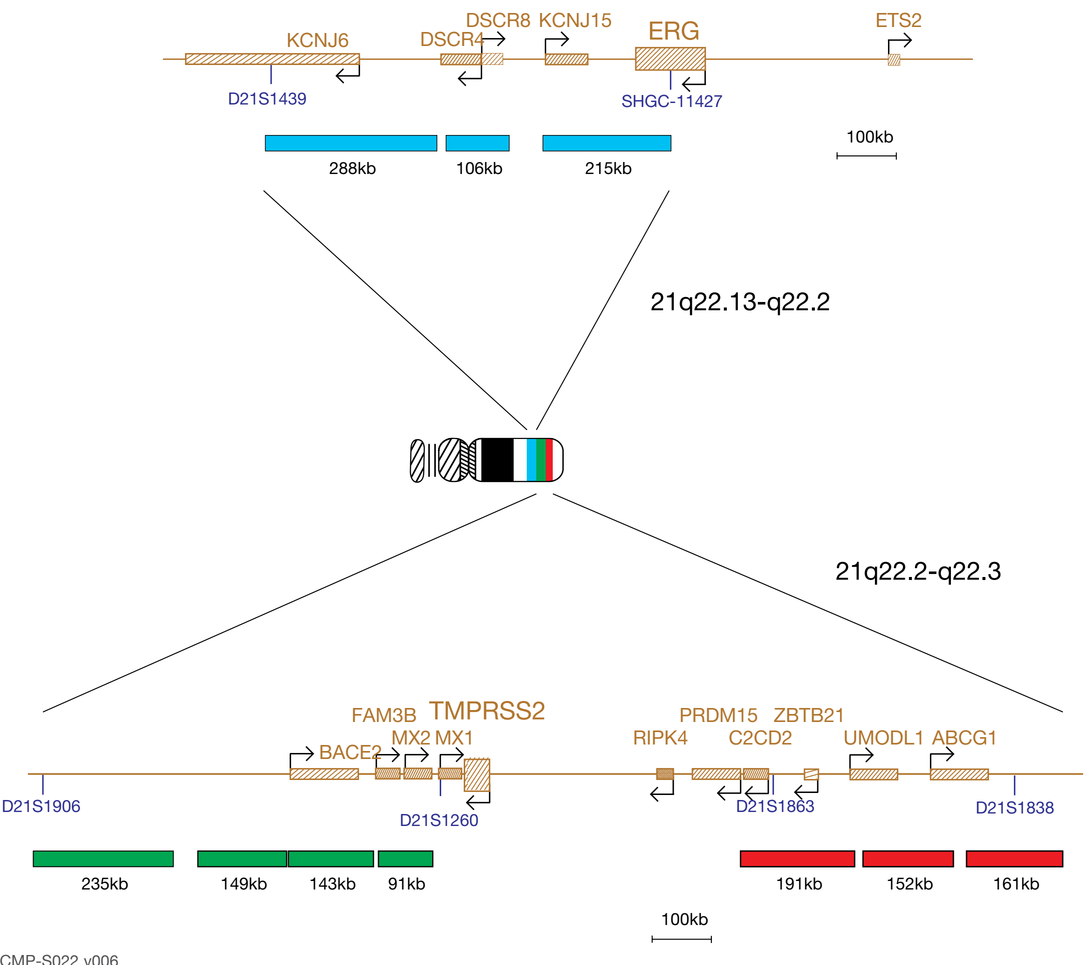
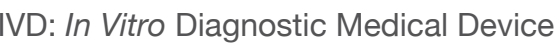
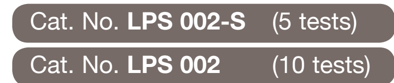
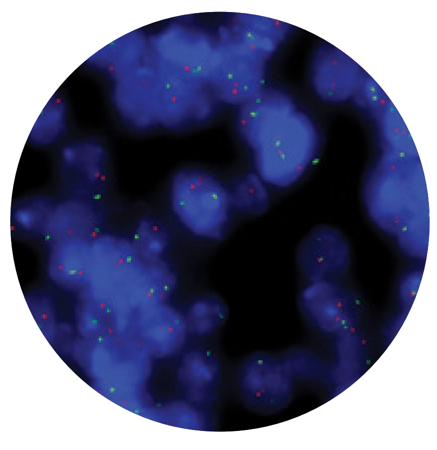


CMP-S022 v006





TOP2A Amplification/Deletion



The TOP2A (*DNA topoisomerase II alpha*) gene at 17q21.2, is located near the ERBB2 oncogene. The TOP2A encoded protein has a function in DNA replication and the transcription of mRNA[1,2]. Amplification of TOP2A gene is seen in breast cancer, frequently with co-amplification of ERBB2[3,4].

In breast cancer, TOP2A gene aberrations are a marker of response to anthracycline-based chemotherapy[5], whilst in epithelial ovarian cancers, TOP2A gain is reported to predict response to pegylated liposomal doxorubicin[6].

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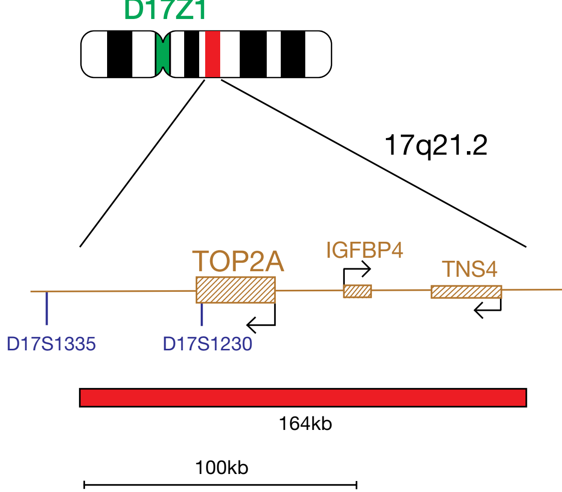
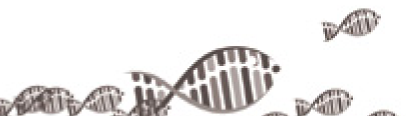


CMP-S019 v003

IVD: *In Vitro* Diagnostic Medical Device



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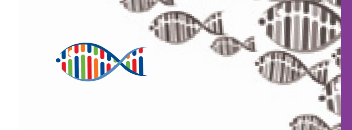
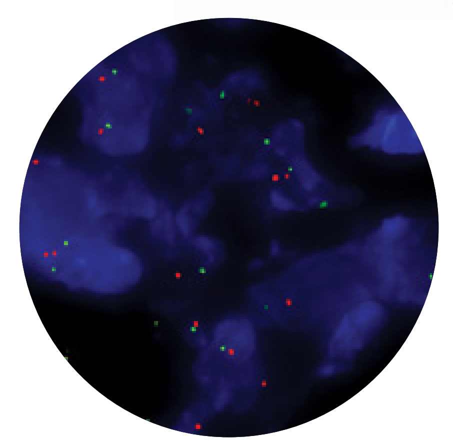
Cat. No. **LPS 005** (10 tests)



ZNF217 Amplification



The ZNF217 (*zinc finger protein 217*) gene at 20q13.2, which functions as a transcription repressor for a variety of genes[1], is frequently amplified in human cancers[2].

ZNF217 amplification has been reported in breast cancer[3,4], in which it has been associated with a poor prognosis[5,6]. It has also been reported in ovarian clear cell carcinoma[4,7,8] in which it correlates with shorter progression-free and overall survival[5,9]. It has been shown that the silencing of ZNF217 inhibits ovarian cancer cell growth and their invasive ability in cancer cell-lines, making it a potential target for future anti-cancer therapies[2,10].

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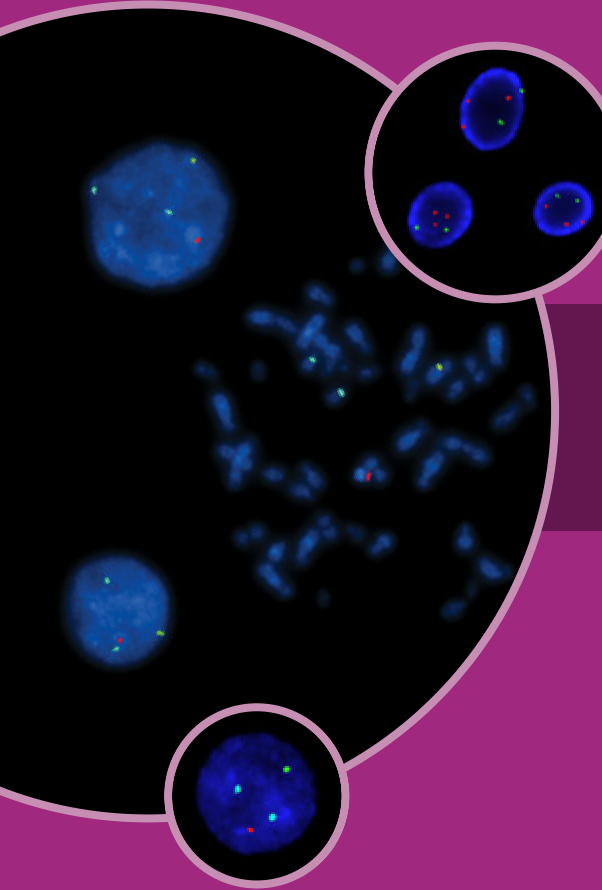
20p13
20q13.2
DEFB128
ZNF217
D20S1156
D20S183
D20S211
D20S840
131kb
197kb
100kb

CMP-S020 v004

IVD: *In Vitro* Diagnostic Medical Device



Prenatal

Contents

Cytocell FISH probes are CE marked IVDs* unless otherwise indicated.

123 Aquarius® *FAST* FISH Prenatal Enumeration Kits (IVD*)
124 Aquarius® Prenatal Enumeration Kits (IVD*)

Prenatal

Cytocell's prenatal fluorescence *in situ* hybridisation (FISH) assays are designed for the rapid and accurate detection of the most common foetal chromosomal disorders.

Trisomy of chromosome 21, resulting in Down syndrome[1], is one of the most common chromosome abnormalities in humans and the risk of having an affected child is known to increase with maternal age[2]. The syndrome represents a particular combination of phenotypic findings, including characteristic facial appearance, a single palmar crease and mental retardation, and may also present with hearing and heart defects. Affected individuals show a highly increased incidence of leukaemia, particularly acute megakaryocytic leukaemia[3].

Trisomy of chromosome 18, resulting in Edwards syndrome, occurs in around 1 in 6000-8000 live births with a female sex bias[4]. The clinical findings are variable, though many exhibit growth delay, heart defects and craniofacial anomalies, as well as possible limb and kidney abnormalities[5].

The rarest trisomy, trisomy 13, responsible for Patau syndrome occurs in approximately 1 in 16,000 newborns[6]. Individuals with Patau syndrome present abnormalities affecting many parts of the body, including the heart, spinal cord, eyes, limbs, face/skull and muscles[6].

Aberrant copy numbers of the X and Y chromosomes can lead to various sex chromosome disorders, such as Klinefelter (47,XXY), Turner (45,X) and other syndromes caused by variations in copy number of X and/or Y. These syndromes have variable incidences and clinical findings[7].

Cytocell Prenatal kits contain fluorescent probes for easy identification of trisomies 21, 18 and 13 present in Down, Edwards and Patau syndrome, respectively, as well as sex chromosome aneuploidies.

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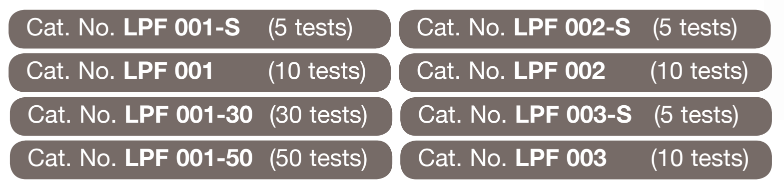
IVD: *In Vitro* Diagnostic Medical Device



Aquarius® *FAST* FISH Prenatal Kits

The Aquarius® *FAST* FISH Prenatal kit allows detection of trisomies 13, 18 and 21 (Patau, Edwards and Down syndromes) and sex chromosome aneuploidies utilising a 2 hour hybridisation protocol.

Aquarius® *FAST* FISH Prenatal kits provide the benefits of:

- 2 hour hybridisation protocol demonstrating high intensity signals and minimal background.
- Economical kit formats: 5, 10, 30** or 50** tests.
- Liquid stable reagents premixed in hybridisation solution and provided with DAPI counterstain.

Each kit contains the probe sets listed below.

Cat. No. **LPF 001**

Probe set 1:

X centromere Xp11.1-q11.1 (DXZ1) Green

Y centromere Yp11.1-q11.1 (DYZ3) Orange

18 centromere 18p11.1-q11.1 (D18Z1) Blue

CMP-A003 v003

CMP-A004 v003

Probe set 2:

13 unique sequence (13q14.2) Green

21 unique sequence (21q22.13) Orange

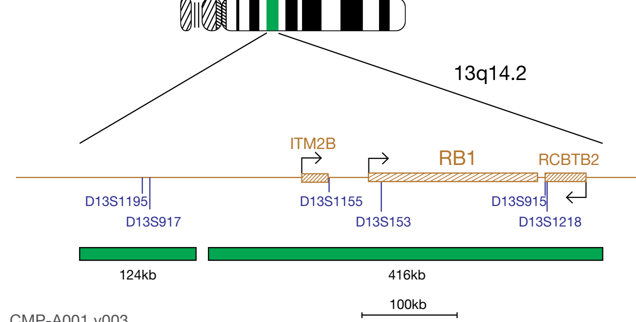
CMP-A005 v003

Cat. No. **LPF 002**

X centromere Xp11.1-q11.1 (DXZ1) Green

Y centromere Yp11.1-q11.1 (DYZ3) Orange

18 centromere 18p11.1-q11.1 (D18Z1) Blue



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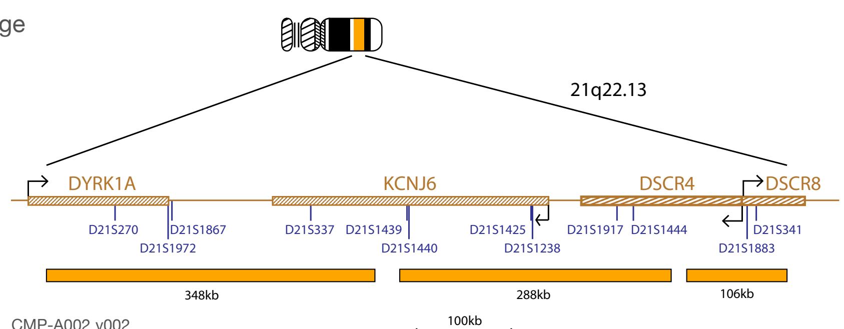


CMP-A002 v002

IVD: *In Vitro* Diagnostic Medical Device
**Not available for LPF002 and LPF003.

Cat. No. **LPA 001-S** (5 tests)	Cat. No. **LPA 002** (10 tests)**
Cat. No. **LPA 001** (10 tests)	Cat. No. **LPA 003** (10 tests)**
Cat. No. **LPA 001-30** (30 tests)	Cat. No. **LPA 004** (10 tests)**
Cat. No. **LPA 001-50** (50 tests)	Cat. No. **LPA 005** (10 tests)**

Aquarius® Prenatal Enumeration Kits

The Aquarius® Prenatal Enumeration range allows detection of trisomies 13, 18 and 21 (Patau, Edwards and Down syndromes) and sex chromosome aneuploidies utilising an overnight hybridisation protocol.

Aquarius® Prenatal kits provide the benefits of:

- Overnight hybridisation protocol demonstrating high intensity signals and minimal background.
- Economical kit formats: 5, 10, 30† or 50† tests.
- Liquid stable reagents premixed in hybridisation solution and provided with DAPI counterstain.

Each kit contains the probe sets listed below.

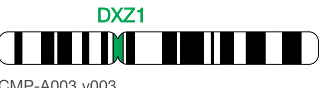
Cat. No. **LPA 001**

Probe set 1:

X centromere Xp11.1-q11.1 (DXZ1) Green

Y centromere Yp11.1-q11.1 (DYZ3) Orange

18 centromere 18p11.1-q11.1 (D18Z1) Blue



CMP-A003 v003

CMP-A004 v003

CMP-A005 v003

Probe set 2:

13 unique sequence (13q14.2) Green

21 unique sequence (21q22.13) Orange

Cat. No. **LPA 002**

X centromere Xp11.1-q11.1 (DXZ1) Green

Y centromere Yp11.1-q11.1 (DYZ3) Orange

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Cat. No. **LPA 003**

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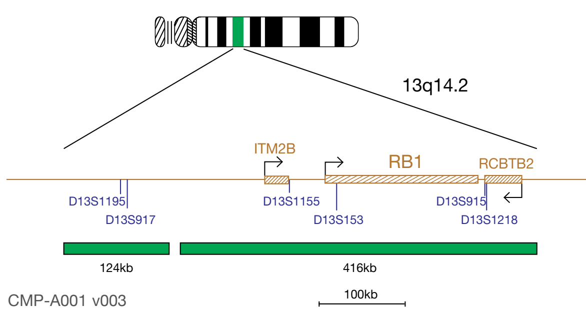
21 unique sequence (21q22.13) Orange



CMP-A001 v003

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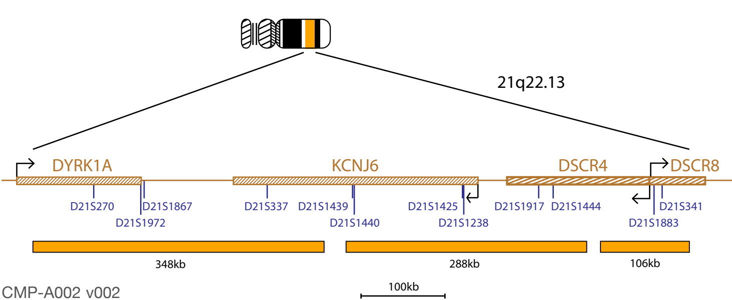
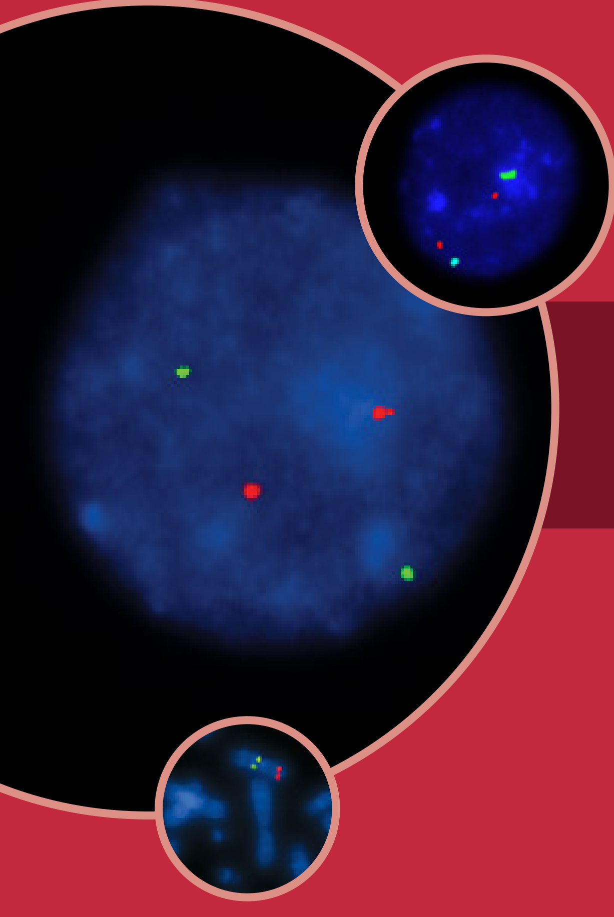
21 unique sequence (21q22.13) Orange



CMP-A002 v002

IVD: *In Vitro* Diagnostic Medical Device

** Also available as 5 tests. † Not available for LPA002, 003, 004 or 005.



Microdeletion

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136 Smith-Magenis (RAI1)/Miller-Dieker Probe Combination

137 SRY

138 Williams-Beuren

139 Wolf-Hirschhorn

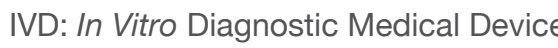
Microdeletion

Microdeletion syndromes are a group of clinically- recognisable disorders brought about by the deletion of specific regions of chromosomal DNA, causing haploinsufficiencies of important genes.

These deletions are difficult to visualise using standard cytogenetic techniques, however fluorescence *in situ* hybridisation (FISH) can resolve these submicroscopic deletions.

Cytocell's comprehensive range of Microdeletion probes features products for some of the rarest human genetic syndromes. With this in mind, we offer all Microdeletion probes in economical five, or standard ten, test kits.

IVD: *In Vitro* Diagnostic Medical Device

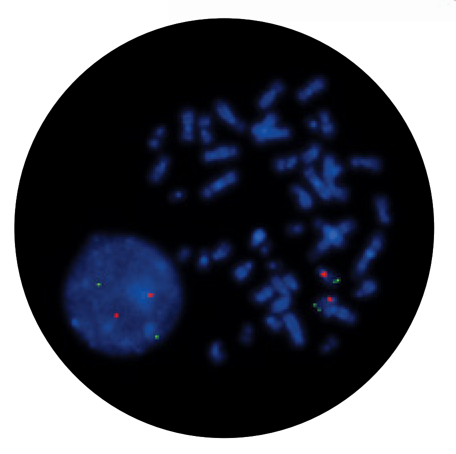


Cytocell aquarius

Cat. No. **LPU 006-S** (5 tests)

Cat. No. **LPU 006** (10 tests)

Angelman (UBE3A/D15S10)



In 70% of patients with Angelman syndrome (AS), a large *de novo* maternal deletion of3-4Mb at 15q11.2-q13 is observed[1,2,3]. The remaining 30% of cases have underlying causes such as paternal uniparental disomy of the same region (~2%), imprinting defects (~2-3%) and mutations of the UBE3A gene[1].

The UBE3A gene lies within the minimum AS critical region[4] approximately 400kb telomeric to the SNRPN gene. It shows preferential expression of the maternal allele in the brain[5] and is mutated in 20-30% of AS patients with normal methylation and biparental contribution of 15q11-q13. It is considered to be one of the causative AS genes[4,5].

The Angelman region probe covers approximately 108kb of genomic DNA, targets most of the UBE3A gene and includes the D15S10 locus. This probe may be used to identify deletions of the AS region, though it will not detect small intragenic deletions or mutations of UBE3A. The probe may also be used to help determine the nature of a Prader-Willi syndrome deletion detected with the SNRPN/Imprinting Centre probe (see LPU005). Large, 3-4Mb deletions of 15q11-13 will cause the deletion of both probe regions (SNRPN/IC and UBE3A/ D15S10). Smaller deletions incorporating the IC and SNRPN, will not cause deletion of the UBE3A/D15S10 probe. These deletions may indicate a much higher risk of recurrence (possibly via grandmatrilineal inheritance) and carriers, and their families, may require further investigation[6].

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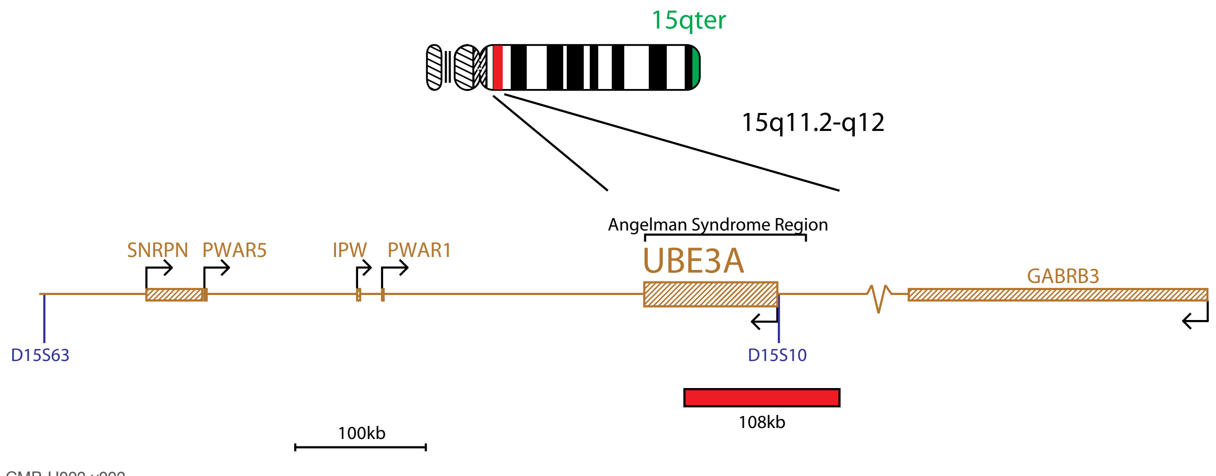

CMP-U002 v002

IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

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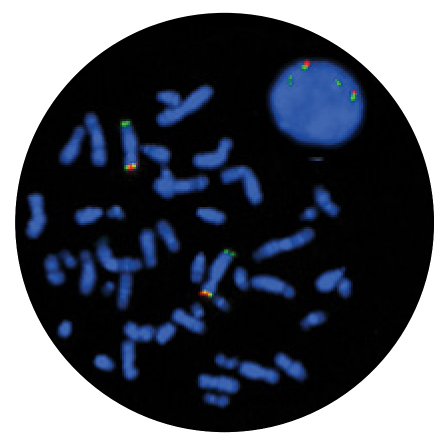

Cri-du-chat and Sotos Probe Combination

Cri-du-chat syndrome consists of multiple congenital anomalies, mental retardation, microcephaly, abnormal face and a mewing cry in infants. Cri-du-chat syndrome is associated with deletions, which vary in size, of part of the short arm of chromosome 5[1].

The estimated prevalence varies between 1 in 20,000 to 1 in 50,000 births[2], making it one of the more common deletion syndromes. A critical chromosomal region involved in the high-pitched cry has been mapped to the proximal part of chromosome band 5p15.3[3]. The region involved in the remaining features of the syndrome has been mapped to 5p15.2[3,4,5].

Sotos syndrome-1 (SOTOS1) is a neurological disorder characterised by a distinctive facial appearance, overgrowth in childhood and developmental delay[6]. Malignant tumour formation has also been reportedly associated with SOTOS1[7].

NSD1, a gene encoding a histone methyltransferase, and implicated in chromatin regulation[8], was identified as the gene disrupted by the 5q35 breakpoint in a patient carrying a chromosomal translocation[9]. The major causes of SOTOS1 are mutations of the NSD1 gene or deletions of the 5q35 region causing haploinsufficiency of the NSD1 gene.

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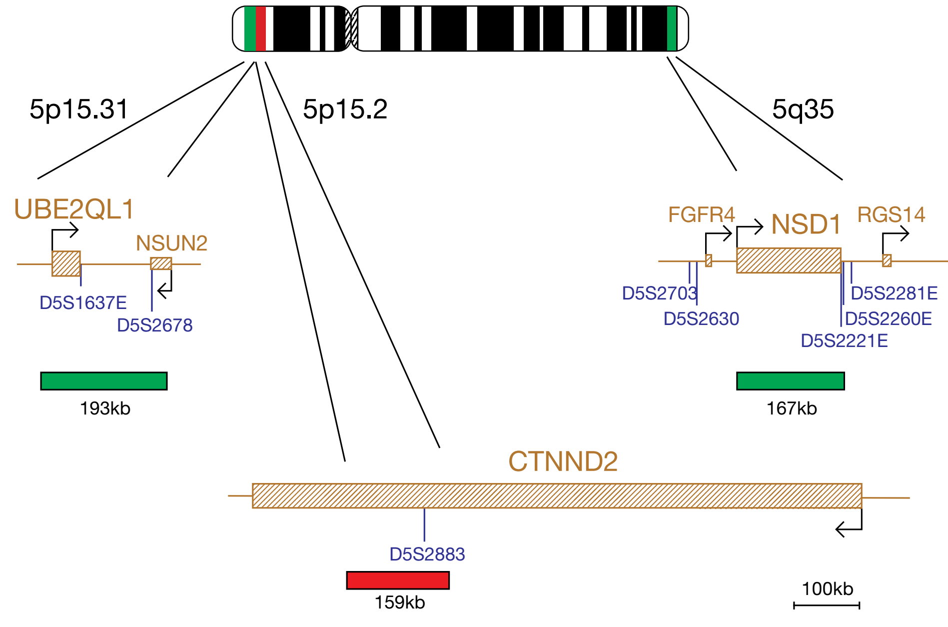

CMP-U004 v002

IVD: *In Vitro* Diagnostic Medical Device

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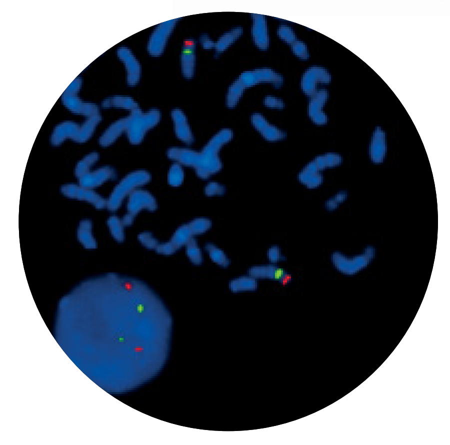
DiGeorge II (10p14)



DiGeorge syndrome[1], and a variety of congenital malformation syndromes including velocardiofacial syndrome (VCFS)[2], share the deletion of chromosome 22 at 22q11.2[2,3,4,5]. These chromosome 22 deletions are collectively coined CATCH22, a mnemonic that covers the clinical findings of Cardiac abnormality, Abnormal facies, Thymic aplasia, Cleft palate and Hypocalaemia/Hyperthyroidism due to a chromosome 22 deletion. In DiGeorge syndrome, however, cases have also been found in which patients have a deletion on chromosome 10p13-p14 (DGS2) instead of chromosome 22[6,7,8].

The deletion of the DGS2 locus on 10p may be 50 times less frequent than that of the DGS1 locus on 22q and has been estimated to occur in 1 in 200,000 live births[9]. The CELF2 gene has been identified within the 300kb minimally deleted region of DGS2 and is postulated to be involved in the DGS2 deletion[10]. CELF2 is a candidate gene for the heart defect and thymus hypoplasia/aplasia associated with partial monosomy 10p[10] and may be involved in atrial septal defects (ASDs), a common cardiac anomaly associated with DGS2[11].

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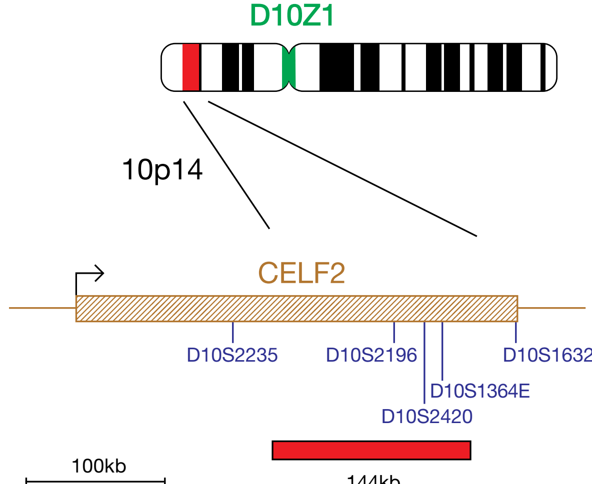

CMP-U005 v002

IVD: *In Vitro* Diagnostic Medical Device

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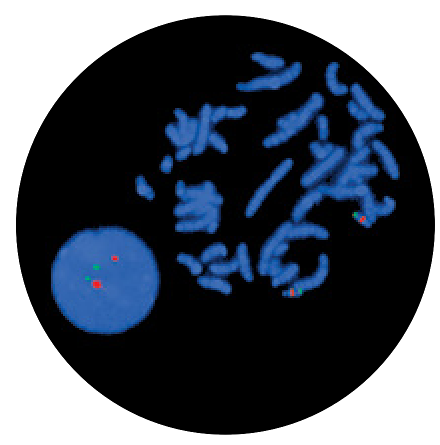
DiGeorge and 22q13.3 Deletion Syndrome Probe Combinations



DiGeorge syndrome

DiGeorge syndrome[1], and a variety of congenital malformation syndromes including velocardiofacial syndrome (VCFS)[2], have in common deletions of chromosome 22 at 22q11.2[2,3,4,5]. These syndomic phenotypes are collectively coined CATCH22, a mnemonic that covers the clinical findings of Cardiac abnormality, Abnormal facies, Thymic aplasia, Cleft palate and Hypocalaemia/Hyperthyroidism due to a chromosome 22 deletion.

In addition, around 29% of nonsyndromic patients with isolated conotruncal defects have been shown to have a 22q11.2 microdeletion[6]. The incidence of these anomalies is estimated to be 1:4000 to 1:9700 live births[7]; therefore deletion of 22q11.2 represent one of the most common genetic defects.

A region of approximately 2Mb, referred to as the DiGeorge Critical Region (DGCR), is the most commonly deleted region and occurs in up to 90% of patients with DiGeorge Syndrome[5,8,9]. Within the DGCR, a minimal critical region of 300-480kb has been described[10,11], containing several genes, including HIRA (TUPLE1), TBX1, SLC25A1 (CTP) and CLTD.

22q13.3 Deletion Syndrome

The 22q13.3 deletion syndrome presents a recognisable phenotype characterised by hypotonia, delay or absence of expressive speech, global developmental delay, normal to accelerated growth and mild dysmorphic features[12,13].

Some deletions of the terminal region of chromosome 22q are cytogenetically visible. However, a few cases of cryptic deletions have been reported[12,14], suggesting that the actual incidence of 22q telomere deletion may be higher than previously thought.

Several observations of patients with 22q13.3 deletion showed that the SHANK3 (ProSAP2)[20] gene, encoding a structural protein of the postsynaptic density of excitation synapses and expressed in the cortex and cerebellum of the brain[15], was disrupted[15,16,17] or deleted[18], making it a candidate causative gene for this syndrome. The deletion varies dramatically in size from 130kb to 9Mb[18,19,20]. The use of 22q subtelomeric probes, distal to the ARSA gene, have therefore been recommended for examining all 22q13.3 deletions[20,21].

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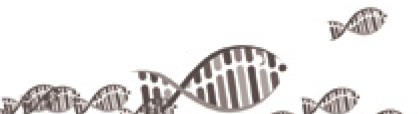
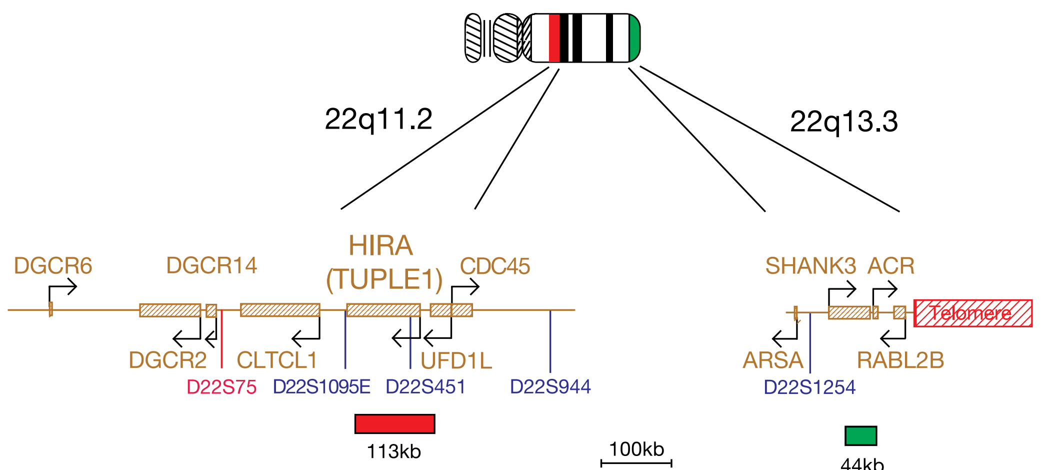
IVD: *In Vitro* Diagnostic Medical Device



VCFS TUPLE 1

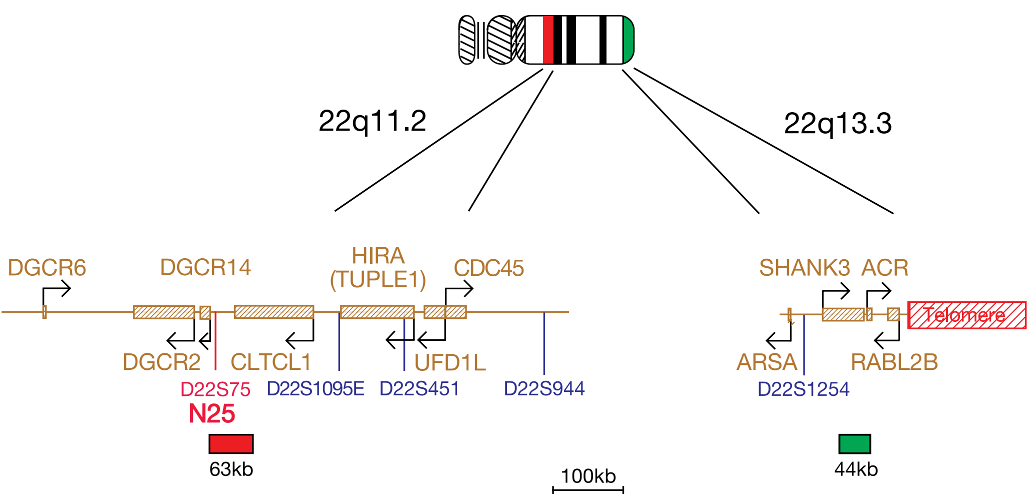
Cat. No. **LPU 004**



CMP-U008 v005

VCFS N25

Cat. No. **LPU 010**



CMP-U007 v003

TBX1

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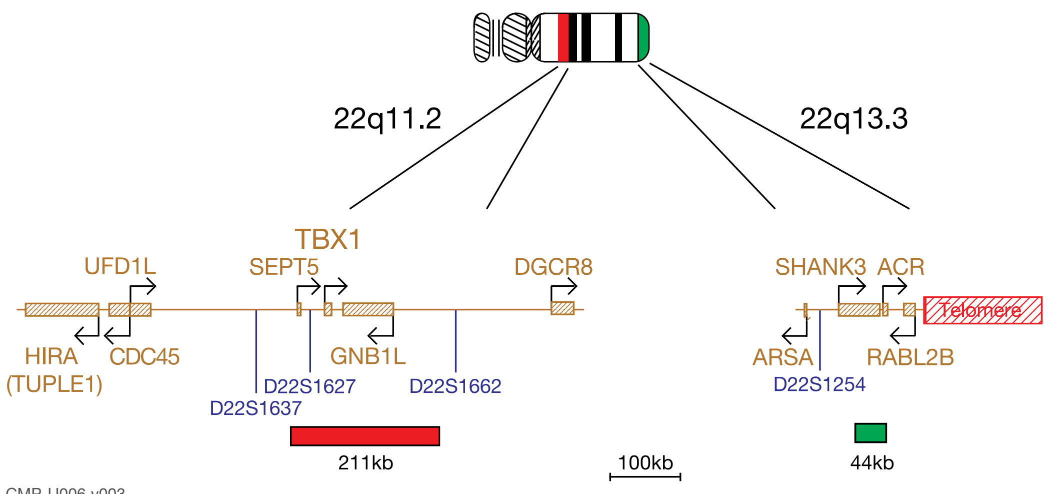
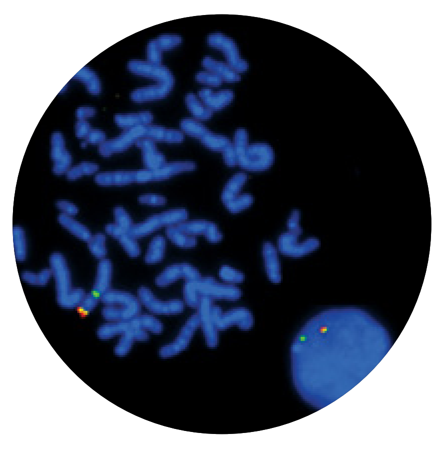


CMP-U006 v003

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPU 016-S** (5 tests)
Cat. No. **LPU 016** (10 tests)

Kallmann (KAL1) and Steroid Sulphatase Deficiency (STS) Probe Combination



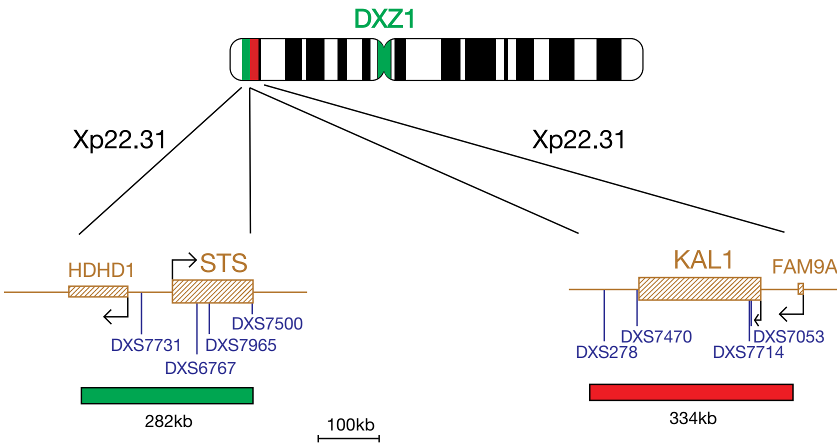
Kallmann syndrome (KS) is a developmental disease characterised by olfactory deficiency[3] and hypogonadotrophic hypogonadism (HH), which is responsible for the absence of spontaneous puberty[1].

Kallmann syndrome is a heterogeneous developmental genetic disorder affecting approximately 1 in 8,000 males and 1 in 40,000 females[2]. Reports indicate three modes of inheritance: X-linked, autosomal dominant and autosomal recessive[1,4].

It has been shown that mutations in the ANOS1 (KAL1) gene at Xp22.3 result in the X-linked form of KS[5]. ANOS1 consists of 14 exons and extends over 200kb and abnormalities of ANOS1 reported in patients with KS include missense and nonsense mutations, splice site mutations, intragenic deletions and submicroscopic chromosomal deletions involving the entire ANOS1 gene[7].

Steroid Sulphatase Deficiency (STS) (also known as X-linked Ichthyosis)[8] is the second most common type of ichthyosis and one of the most frequent human enzyme deficiency disorders.

Deficiency of the STS enzyme is known to be responsible for dark, adhesive and regular scaling of the skin[9]. The gene encoding this protein maps to the distal short arm of chromosome X, which escapesX-chromosome inactivation and has the highest ratio of chromosomal deletions among all genetic disorders[10]. Complete deletions of the STS gene have been found in more than 90% of patients[11]. The deletions can extend to involve neighbouring genes, causing contiguous gene defects. Therefore, STS may be associated with KS[12].



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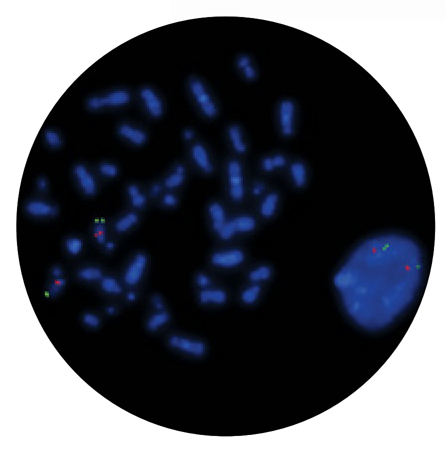
CMP-U009 v002

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPU 005-S** (5 tests)
Cat. No. **LPU 005** (10 tests)

Prader-Willi/Angelman (SNRPN)

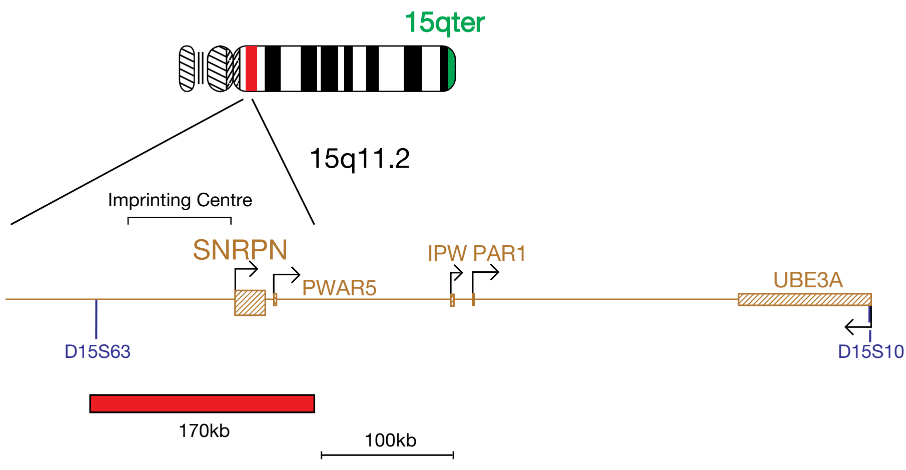


Prader-Willi Syndrome (PWS) and Angelman Syndrome (AS) are distinct neurogenetic disorders caused by the loss of function of genes on chromosome 15 (bands 15q11-13), on either the paternally or maternally inherited chromosome, respectively[1].

In 70% of patients, a large interstitial deletion of 3-4Mb is observed[1,2]. In around 3% of patients, an imprinting defect is observed, caused by either an epimutation or a microdeletion of the Imprinting Centre (IC)[1,3]. Uniparental disomy, in which both chromosome 15s are inherited from the same parent, accounts for most of the remaining patients with PWS/AS[1].

The SNRPN gene is one of four imprinted loci that are expressed from the paternal chromosome 15 region (15q11-13) and maps to the minimally deleted region (MDR) involved in PWS[5]. Its chromosomal location and imprinting status suggest it plays a possible role in the aetiology of PWS[4].

The imprinting centre (IC) maps to a 100kb region proximal to SNRPN. Parental deletions or mutations in the IC impair the imprinting process in 15q11-13 and cause one of two distinct diseases in their offspring[5,6]. Most of the PWS imprinting deletions involve SNRPN and are approximately 200kb in size. The AS imprinting deletions are small (approximately 40kb), involve the BD3 region, and do not include SNRPN.



CMP-U013 v002

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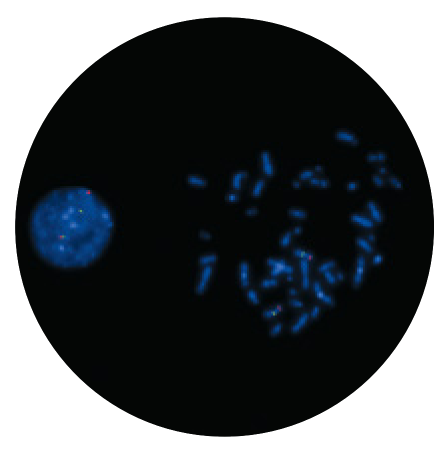
IVD: *In Vitro* Diagnostic Medical Device

Cytocell aquarius

Cat. No. **LPU 024-S** (5 tests)
Cat. No. **LPU 024** (10 tests)

Saethre-Chotzen/Williams-Beuren Combination



Saethre-Chotzen syndrome is a rare, congenital, autosomal dominant disorder characterised by craniofacial and limb abnormalities[1].

The incidence of this syndrome is estimated to be 1 in 25,000-50,000 live births, though due to the phenotype often being very mild, it is possible that the syndrome is under diagnosed[1]. The identification of TWIST1 (a basic helix-loop-helix transcription factor on chromosome band 7p21.1) as a causative gene[2,3] has proved invaluable for the diagnosis of this phenotypically variable disorder[1].

Williams-Beuren Syndrome (WBS) is a rare neurodevelopmental disorder caused by a deletion (approx. 1.5-1.8Mb in size, containing around 28 genes[6]) within chromosome band 7q11.23[4]. The incidence of this syndrome is estimated at 1 in 7,500 to 20,000 live births[5,6].

Patients display a distinctive 'elfin' facial appearance, connective tissue problems, SupravalVular Aortic Stenosis (SVAS), growth retardation, renal anomalies, transient hypercalcaemia, hyperacusis and mental retardation[7]. Haploinsufficiency or hemizygosity of the elastin (ELN) gene has been identified as being responsible for the SVAS[8,9] but none of the other clinical features of the syndrome have been unequivocally attributed to specific genes within the WBS deleted region. These genotype-phenotype correlations are made more difficult in WBS patients as the deletion has also been shown to have an effect on normal copy number genes that neighbour the deletion breakpoints[10].

The Saethre-Chotzen/Williams-Beuren Combination contains a red probe that covers the TWIST1 gene for Saethre-Chotzen syndrome and a green probe covering the area around the ELN gene in the Williams-Beuren syndrome deleted region.

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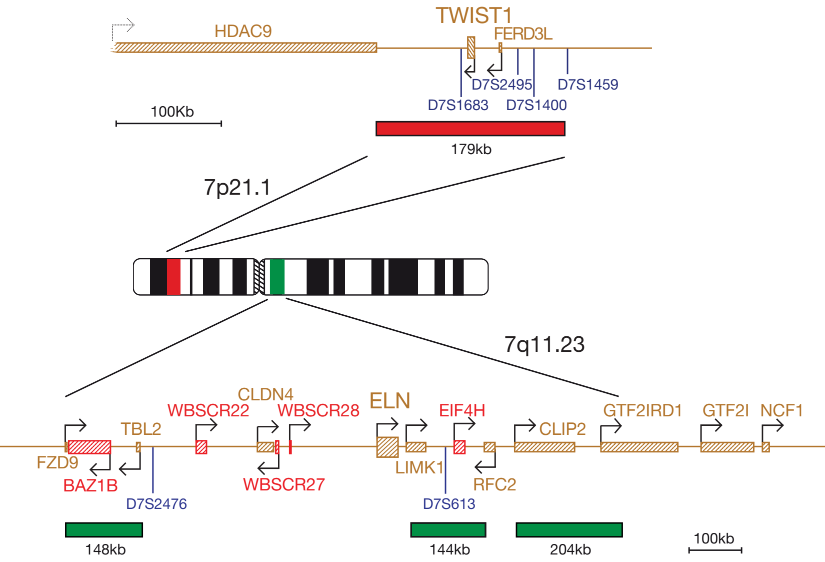
10. Merla *et al*., Am J Hum Genet 2006; 79:332-341



CMP-U015 v002

IVD: *In Vitro* Diagnostic Medical Device

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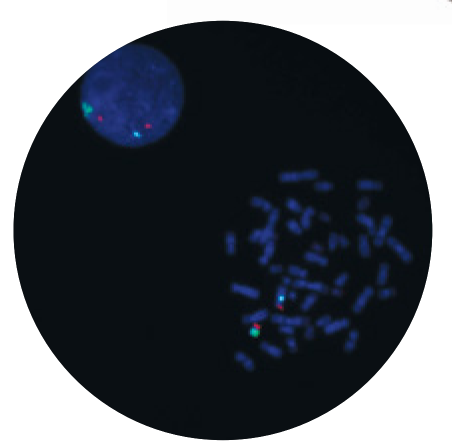
Cat. No. **LPU 025** (10 tests)



SHOX

The SHOX (short stature homeobox) gene is located in the pseudoautosomal region (PAR1) of chromosomes X and Y, in bands Xp22.33 and Yp11.32[1].

The gene encodes a transcription factor of 292 and 225 amino acids (SHOXa and SHOXb respectively), whose translated proteins differ in the C-terminal regions. SHOX is a cell-specific homeodomain protein involved in cell cycle and growth regulation and activates transcription in osteogenic cells[2]. SHOX haploinsufficiency is involved in the aetiology of idiopathic short stature and the short stature observed in Turner syndrome[3]. Homozygous loss of the SHOX gene has been correlated with Langer type mesomelic dysplasia. Subsequently, heterozygous SHOX mutations were also shown to cause Leri-Weill dyschondrosteosis[4].

The incidence of SHOX deficiency is between 1 in 2000 and 1 in 5000 in the general population and between 1 in 40 and 1 in 150 in patients with idiopathic short stature[5,6].

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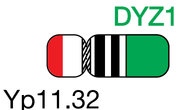

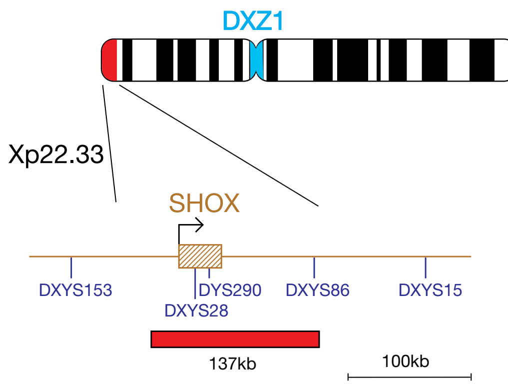

CMP-U016 v003

IVD: *In Vitro* Diagnostic Medical Device

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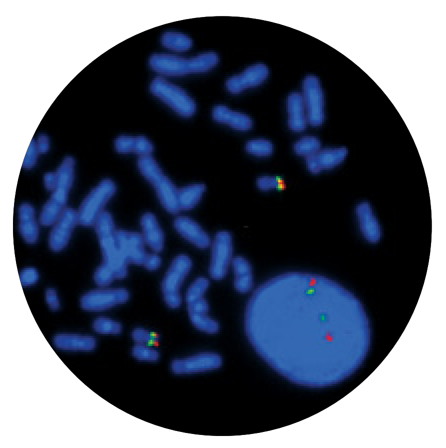


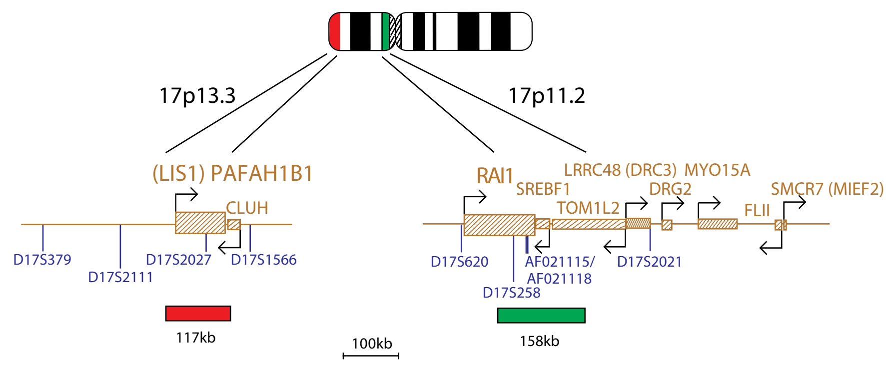
Smith-Magenis (RAI1)/ Miller-Dieker Probe Combination

Smith-Magenis syndrome (SMS) is a multiple congenital anomaly syndrome characterised by mental retardation, neurobehavorial abnormalities, sleep disturbances, short stature, minor craniofacial and skeletal anomalies, congenital heart defects and renal anomalies[1,2].

It is one of the most frequently observed human microdeletion syndromes and is associated with an interstitial deletion of the chromosome band 17p11.2[2]. Molecular studies in SMS patients suggest a minimally deleted region (MDR) spanning approximately 700kb[3,5], though the common deletion is around 4Mb in size[4]. The proximal boundary of the MDR is within a region of overlap between the FLII and LLGL1 genes, and the distal boundary within the PEMT gene[3]. Deletions or mutations in RAI1 (Retinoic Acid Induced 1) gene, which lies within the MDR, are associated with the syndrome[3,5,6,7]. RAI1 was shown to be the primary gene responsible for most features of SMS[8,9].

Miller-Dieker syndrome (MDS) is a multiple malformation characterised by classical lissencephaly, a characteristic facial appearance and sometimes other birth defects[11]. It is associated with visible or submicroscopic rearrangements within chromosome band 17p13.3 in almost all cases[12]. Isolated lissencephaly sequence (ILS) consists of classical lissencephaly with no other major anomalies[13]. Submicroscopic deletions of chromosome 17p13.3 have been detected in almost 40% of these patients[12].

MDS is considered a contiguous gene deletion syndrome where deletion of physically contiguous genes leads to the complex phenotypic abnormalities observed. The PAFAH1B1 (LIS1) gene is located at 17p13.3 and is recognised as the causative gene for the lissencephaly phenotype in both MDS and ILS[14,15]. Deletions in MDS patients always include the PAFAH1B1 gene, together with other telomeric loci to a distance in excess of 250kb[14].



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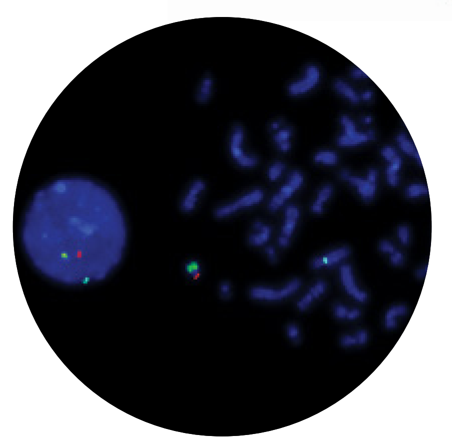
CMP-U017 v002

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPU 026-S** (5 tests)
Cat. No. **LPU 026** (10 tests)

SRY



The mammalian Y-chromosomal testis-determining gene SRY (*sex determining region Y*), located in band Yp11.31, induces male sex determination[1].

It encodes a transcription factor that is a member of the high mobility group (HMG)-box family of DNA binding proteins[2]. In mammals, it triggers the development of undifferentiated gonads into testes[3]. Human zygotes with mutations in SRY develop into XY females, while XX zygotes in the presence of SRY develop a male phenotype with occasional ambiguous genitalia[4,5]. Deletions and translocations involving the SRY region are implicated in disorders of sex differentiation[6].

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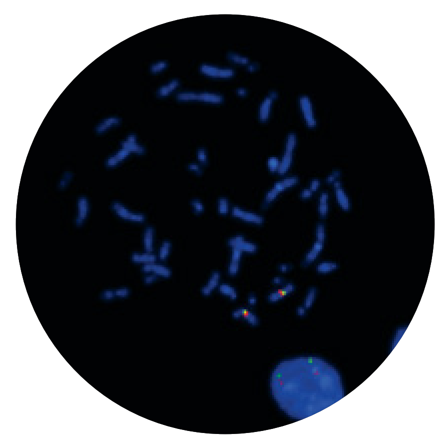
DYZ1
DXZ1
Yp11.31
CD99
PAR
SRY
RH38681
DYS376
DYS242
RPS4Y1
DYS234
ZFY
30kb
50kb
100kb

CMP-U019 v003

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPU 011-S** (5 tests)
Cat. No. **LPU 011** (10 tests)

Williams-Beuren



Williams-Beuren Syndrome (WBS) is a rare neurodevelopmental disorder caused by a deletion (approximately 1.5-1.8Mb in size, containing around 28 genes) within chromosome band 7q11.23[1]. The incidence of this syndrome is estimated at 1 in 7,500 to 20,000 live births[2,3,4].

Patients display a distinctive 'elfin' facial appearance, connective tissue problems, supravalvular aortic stenosis (SVAS), growth retardation, renal anomalies, transient hypercalcaemia, hyperacusis and mental retardation[5]. Haploinsufficiency of the elastin (ELN) gene has been identified as being responsible for the SVAS[6,7] but none of the other clinical features of the syndrome have been unequivocally attributed to specific genes within the WBS deleted region. These genotype-phenpotype correlations are made more difficult in WBS patients as the deletion has also been shown to have an effect on normal copy number genes that neighbour the deletion breakpoints[8].

REFERENCES

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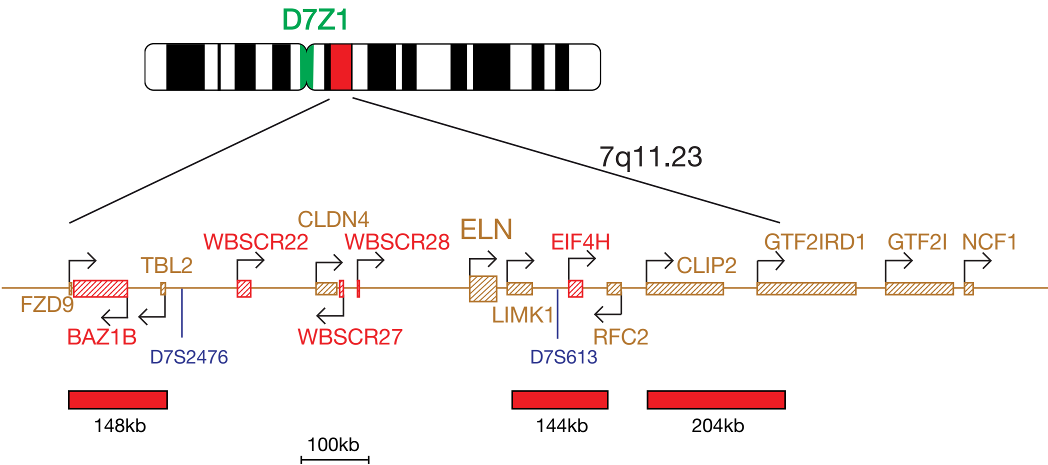
7. Tassabehji M *et al*., Hum Mol Genet 1997;6:1029-36
8. Merla *et al*., Am J Hum Genet 2006; 79:332-341



CMP-U020 v002

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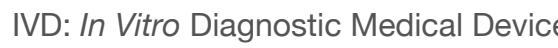
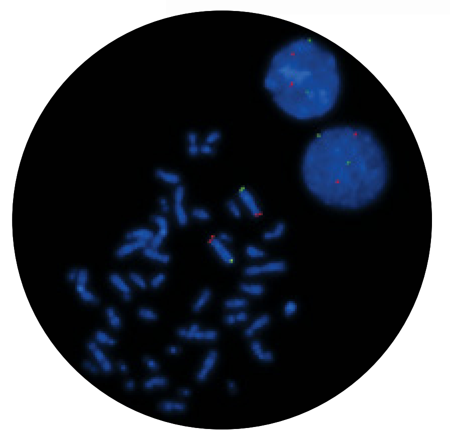


Cat. No. **LPU 009-S** (5 tests)
Cat. No. **LPU 009** (10 tests)

Wolf-Hirschhorn

Wolf-Hirschhorn syndrome is a multiple malformation syndrome characterised by severe growth deficiency, severe to profound mental retardation with the onset of convulsions in early infancy, microcephaly, sacral dimples and a characteristic face ('Greek helmet appearance')[1,2].

The phenotype results from the partial deletion of the short arm of chromosome 4 (4p16.3). Molecular analyses of patients with small terminal and interstitial deletions have allowed the definition of the Wolf-Hirschhorn Critical Region, which is 165kb in size and lies between D4S166 and D4S3327[3].



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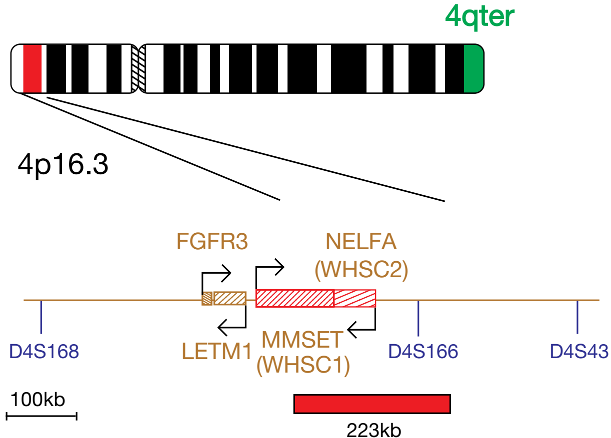
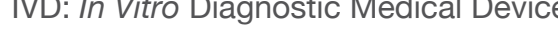
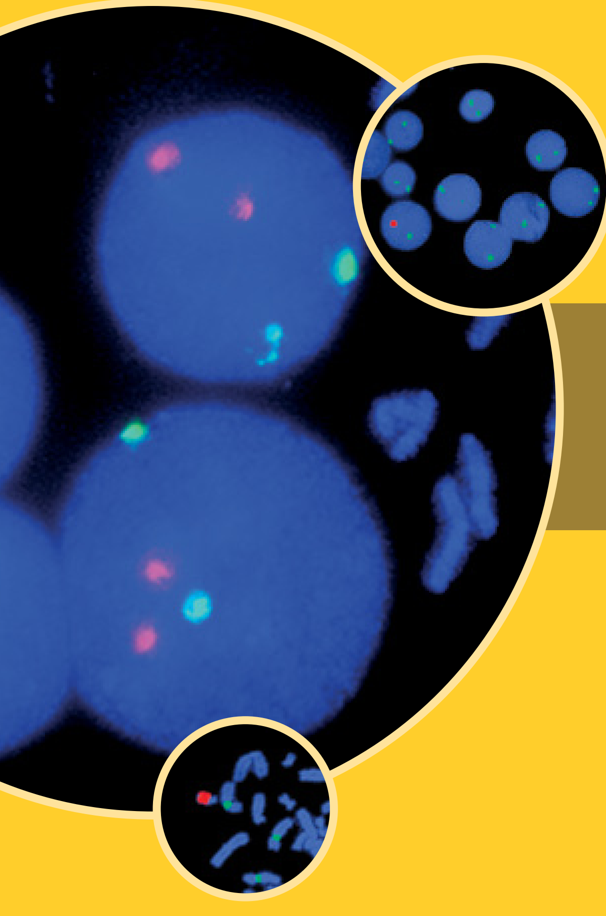


CMP-U021 v004



IVD: *In Vitro* Diagnostic Medical Device



Satellites

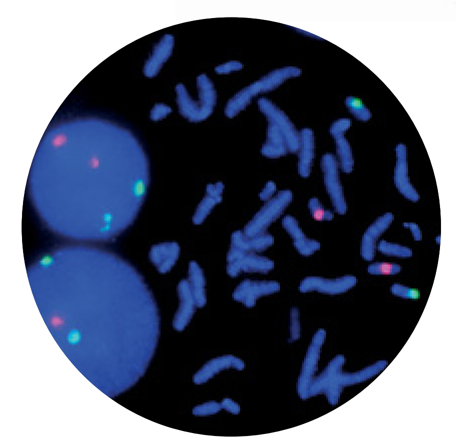
Contents

Cytocell FISH probes are CE marked IVDs* unless otherwise indicated.

143 Satellite Enumeration Probes
144 Blue Labelled Satelite Enumeration Probes
144 Dual Labelled Satellite Probe Sets
145 Acro-P-Arm Probe

IVD: *In Vitro* Diagnostic Medical Device

Satellite Enumeration Probes



Cytocell's Satellite Enumeration probes are chromosome specific sequences generated from highly repeated human satellite DNA located in the centromeric, pericentromeric or heterochromatic regions of each chromosome.

These probes allow rapid identification and enumeration of human chromosomes in interphase and metaphase cells of postnatal samples. Cytocell offers a complete range of satellite probes available in the Aquarius® liquid format. The probes are available independently and directly labelled in either red or green. They are produced in a concentrated form to allow the mixing, if required, of up to three satellite probes in the same hybridisation.

The kits are supplied in an economical 5 test format and come complete with hybridisation solution and DAPI counterstain.

Green Satellite Enumeration Probes

- Cat. No. **LPE 001G**
- Cat. No. **LPE 002G**
- Cat. No. **LPE 003G**
- Cat. No. **LPE 004G**
- Cat. No. **LPE 005G** (Chromosome 1,5,19)
- Cat. No. **LPE 006G**
- Cat. No. **LPE 007G**
- Cat. No. **LPE 008G**
- Cat. No. **LPE 009G**
- Cat. No. **LPE 010G**
- Cat. No. **LPE 011G**
- Cat. No. **LPE 012G**
- Cat. No. **LPE 013G** (Chromosome 13,21)
- Cat. No. **LPE 014G** (Chromosome 14,22)
- Cat. No. **LPE 015G**
- Cat. No. **LPE 016G**
- Cat. No. **LPE 017G**
- Cat. No. **LPE 018G**
- Cat. No. **LPE 020G**
- Cat. No. **LPE 0XG**
- Cat. No. **LPE 0YcG**
- Cat. No. **LPE 0YqG**

Red Satellite Enumeration Probes

- Cat. No. **LPE 001R**
- Cat. No. **LPE 002R**
- Cat. No. **LPE 003R**
- Cat. No. **LPE 004R**
- Cat. No. **LPE 005R** (Chromosome 1,5,19)
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- Cat. No. **LPE 008R**
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- Cat. No. **LPE 010R**
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- Cat. No. **LPE 012R**
- Cat. No. **LPE 013R** (Chromosome 13,21)
- Cat. No. **LPE 014R** (Chromosome 14,22)
- Cat. No. **LPE 015R**
- Cat. No. **LPE 016R**
- Cat. No. **LPE 017R**
- Cat. No. **LPE 018R**
- Cat. No. **LPE 020R**
- Cat. No. **LPE 0XR**
- Cat. No. **LPE 0YcR**
- Cat. No. **LPE 0YqR**

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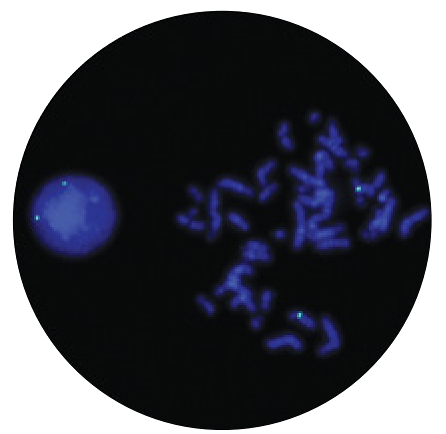
Cytocell aquarius

Cat. No. **LPE 008B** (10 tests) Cat. No. **LPE 012B** (10 tests) Cat. No. **LPE 017B** (10 tests)

Blue Labelled Satellite Enumeration Probes



Cytocell also offers a limited range of satellite probes directly labelled in a blue fluorophore. The probes are produced in a concentrated form to allow the mixing, if required, of up to 3 satellite probes in the same hybridisation. The kits are supplied in a 10 test format and come complete with hybridisation solution and DAPI counterstain.

- Chromosome 8
- Chromosome 12
- Chromosome 17

Other chromosomes are available through the myProbes® custom FISH probes program

IVD: *In Vitro* Diagnostic Medical Device

Cat. No. **LPE 0XYc** Cat. No. **LPE 0XYq**

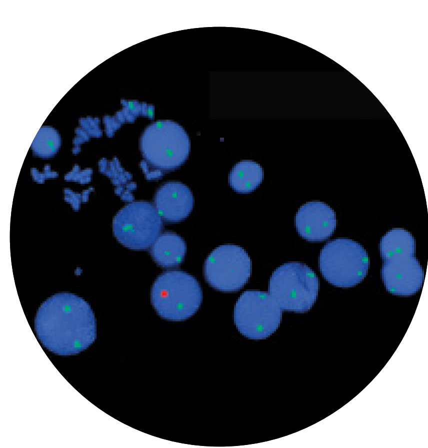
Dual Labelled Satellite Probe Sets

We also offer two dual labelled X and Y probe sets, available in the Aquarius® liquid range in a 10 test format. These may be used to identify human X and Y chromosomes in both interphase and metaphase cells.

XYc: Xp11.1-q11.1 directly labelled with a green fluorophore and Yp11.1-q11.1 with a red fluorophore.

XYq: Xp11.1-q11.1 directly labelled with a green fluorophore and Yq12 with a red fluorophore.

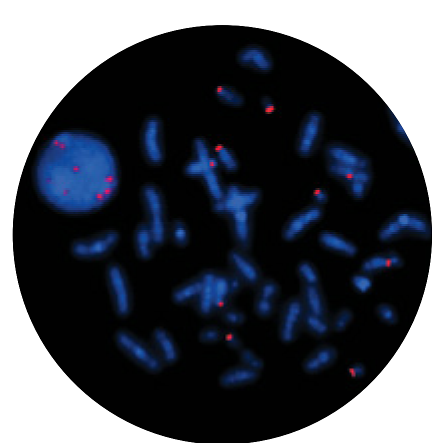
These probes are designed for use on cultured peripheral blood and bone marrow cells.



XYq probe
(patient after sex-mismatched bone marrow transplant)

IVD: *In Vitro* Diagnostic Medical Device

Acro-P-Arm Probe



The Nucleolar Organiser Regions (NOR) contain clusters of genes which code for the three largest structural rRNA molecules (5.8S, 18S and 28S).

These rRNA genes are critically important for the viability of the cell and represent around 0.5% of the human diploid genome. They are found in the short arm of the acrocentric chromosomes and are the region around which the nucleoli develop at the end of mitosis[1].

In routine cytogenetic analysis, NOR can be used to delineate marker chromosomes through a process of silver staining the NOR (known as AgNOR staining[2]). However, the technique relies on translation of protein and if this is not present, conventional silver staining will not stain the NOR. Cytocell's FISH probe has been developed to overcome this problem so that presence of the acrocentric chromosomes in the marker can be detected.

REFERENCES

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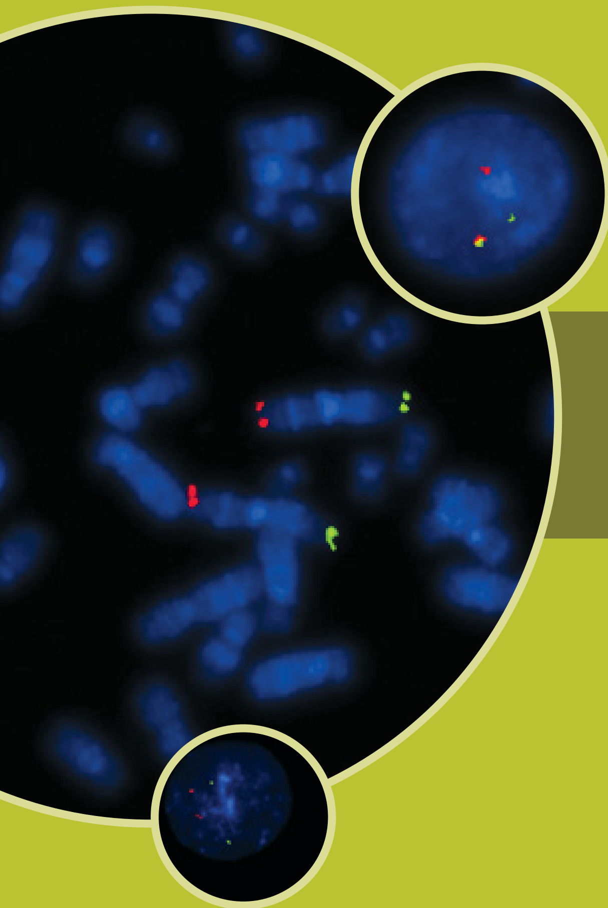
IVD: *In Vitro* Diagnostic Medical Device



Subtelomeres

Contents

Cytocell FISH probes are CE marked IVDs* unless otherwise indicated.

149 Aquarius® Subtelomere Specific Probes
150 Aquarius® TeloMark Probes

Subtelomere Specific Probes

Chromosomal rearrangements involving the ends of chromosomes have emerged as an important cause of genetic disease given the gene-rich nature of the regions adjacent to the telomeres[1]. The importance of such subtelomeric chromosome rearrangements has been clearly shown by their observed association with unexplained mental retardation and congenital abnormalities[2].

Individual subtelomere specific probes have been used to focus on particular subtelomeric regions and have resulted in the establishment of syndromes such as the chromosome 1p36 deletion syndrome[3,10] and the 22q13.3 deletion syndrome[4]. The probes are also finding applications in the investigation of autistic disorders[5], recurrent miscarriages[6] and haematological malignancies[7].

Cytocell's subtelomere specific probes are located in the most distal region of chromosome specific DNA on each chromosome. Beyond this unique sequence material is the 100 to 300kb region of telomere associated repeat followed by the cap of between 3 to 20kb of tandemly repeated (TTAGGG)n sequence[8].

The probes have been chosen from the most distal unique sequence to provide the best possible specificity, whilst also being applicable for routine use for the examination of subtelomeric enumeration and integrity.

The original second-generation set of probes is derived from PAC clones[9] and was established in conjunction with the Institute of Molecular Medicine, part of Oxford University, in the UK[11]. Continuing product improvements have led to some substitutions with alternative cosmid (35-40kb) or BAC (150kb) clones to give improved signal strength or chromosome specificity.

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1. Saccone S *et al*., Proc Natl Acad Sci USA 1992;89:4913-7
2. Flint J *et al*., Nat Genet 1997;15(3):252-7
3. Heilstedt HA *et al*., Clin Genet 2003;64(4):310-6
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5. Wolff DJ *et al*., Genet in Med 2002;4(1):10-4
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8. Moyzis RK *et al*., Proc Natl Acad Sci USA 1988;85:6622-6
9. Knight SJL *et al*., Am J Hum Genet 2000;67:320-32
10. Institute of Molecular Medicine and National Institute of Health Collaboration, Nat Genet 1997;14:86-9

IVD: *In Vitro* Diagnostic Medical Device

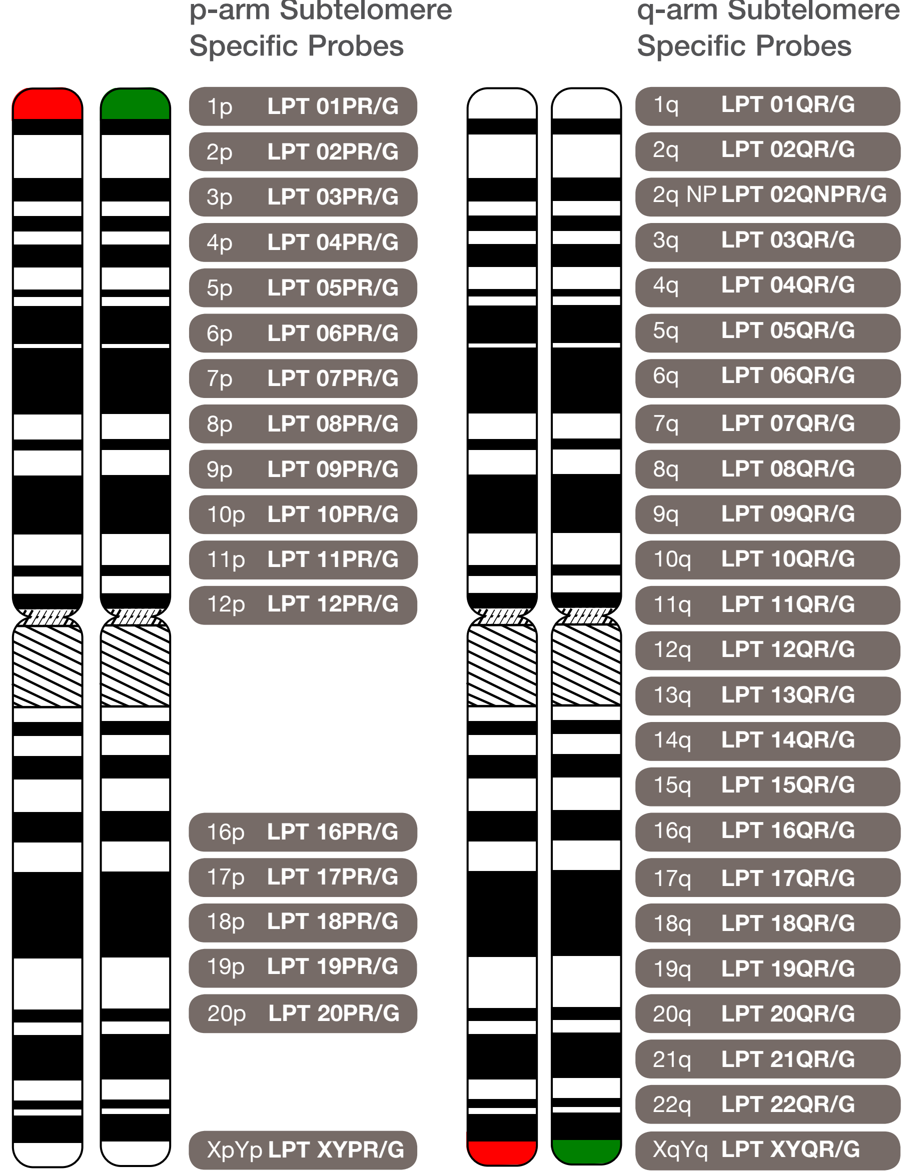
Aquarius® Subtelomere Specific Probes

Cytocell also offers a complete set of subtelomere specific probes available in the Aquarius® liquid format. The set identifies 41 of the 46 human subtelomeres with the exclusion of the p-arm telomeres of the acrocentric chromosomes.

The probes are available independently and directly labelled in either a red or a green fluorophore (Texas Red® or FITC spectra respectively).

The probes are supplied in an economical 5 test format and are concentrated to allow the mixing, if required, of up to three Aquarius® subtelomere specific probes in the same hybridisation.

The kits come complete with hybridisation solution, DAPI counterstain and full instructions for use. For probe specifications, please refer to the Aquarius® Subtelomere Specific Probe Range Summary chart in the Index section.



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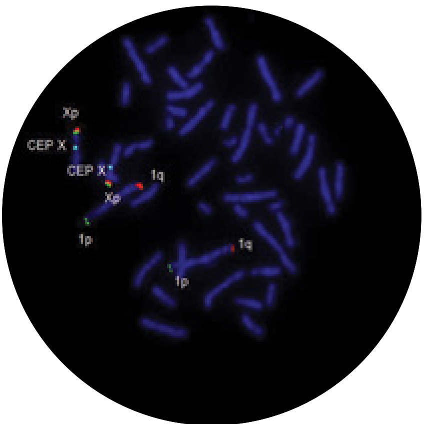
Aquarius® TeloMark Probes

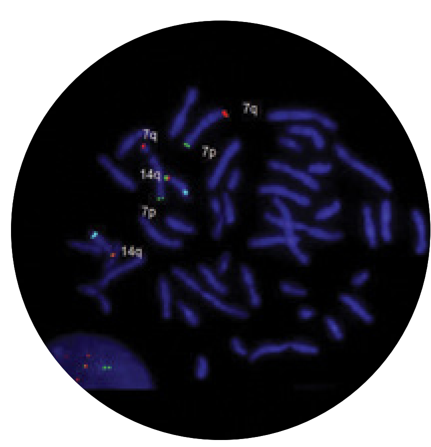
Subtelomere FISH analysis is commonly used as an adjunct to routine cytogenetic testing in order to detect small rearrangements involving the telomeric regions of chromosomes. Patients can be referred for telomere analyses for a number of different reasons, including genetic disease, autistic disorders, unexplained mental retardation/developmental delay, recurrent miscarriages and haematological malignancies[1-4].

The Cytocell TeloMark kit consists of 41 subtelomere specific probes, three centromere and six locus specific probes (50 different probes in total). The subtelomere probes represent all chromosome ends apart from the p-arms of the five acrocentric chromosomes and with no distinction between the X and Y due to clones being located in the pseudoautosomal regions. All of these probes map to unique regions of the chromosomes, within 850kb of the true telomere.

The probes in TeloMark are provided as fifteen separate mixes, either provided individually or as a kit containing all fifteen. All probes are directly labelled in orange, green, yellow (orange and green combined) or blue.



TeloMark Mix 01



TeloMark Mix 07

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2. Knight *et al*., Am. J. Hum. Genet. 2000; 67:320-332
3. Knight *et al*., Eur. J Hum. Genet. 1997 Jan-Feb;5(1):1-8
4. Ravan *et al*., J Med Genet. 2006;43:478-489

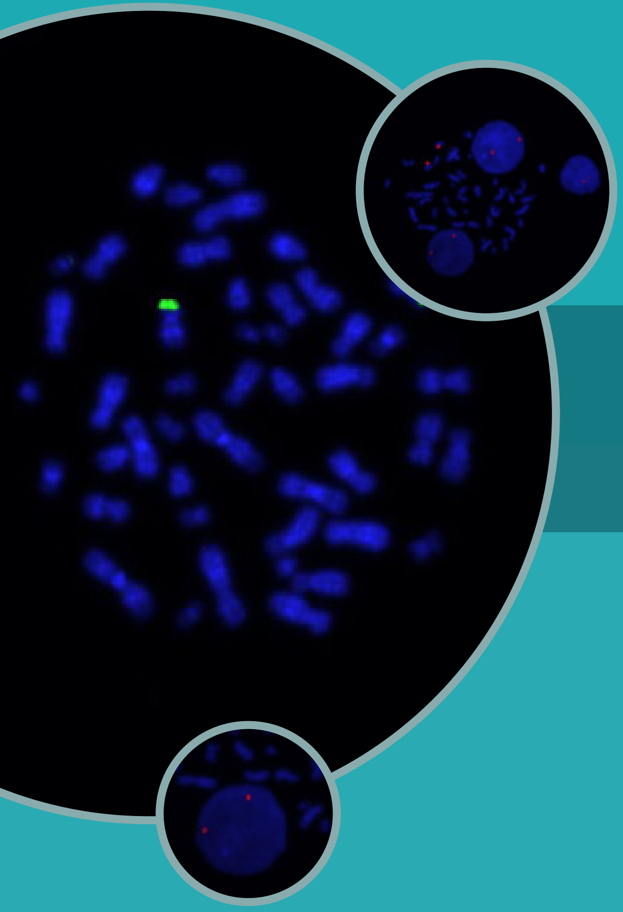
IVD: *In Vitro* Diagnostic Medical Device

TeloMark Product Kit

Probe Name	No. Tests	Cat. No.*
TeloMark Kit (Contains Mixes 1-15)	5 or 10	LPT MRK

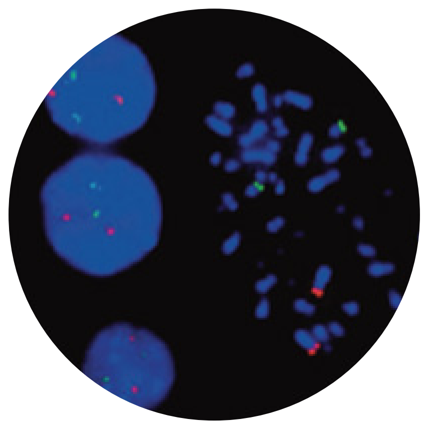
Telomark Mix	Probes	No. tests	Cat. no.*
Mix 01	1p in Green, 1q in Orange, Xp/Yp in Orange and Green (Yellow), DXZ1 in Blue	5 or 10	LPT MRK01
Mix 02	2p in Green, 2q in Orange, Xq/Yq in Orange and Green (Yellow), DXZ1 in Blue	5 or 10	LPT MRK02
Mix 03	3p in Green, 3q in Orange, 22q in Orange and Green (Yellow), BCR (22q11) in Blue	5 or 10	LPT MRK03
Mix 04	4p in Green, 4q in Orange, 21q in Orange and Green (Yellow), AML1 (RUNX1) (21q22) in Blue	5 or 10	LPT MRK04
Mix 05	5p in Green, 5q in Orange	5 or 10	LPT MRK05
Mix 06	6p in Green, 6q in Orange, 13q in Orange and Green (Yellow), 13q14 in Blue	5 or 10	LPT MRK06
Mix 07	7p in Green, 7q in Orange, 14q in Orange and Green (Yellow), TCRAD (14q11.2) in Blue	5 or 10	LPT MRK07
Mix 08	8p in Green, 8q in Orange, 17p in Orange and Green (Yellow), D17Z1 in Blue	5 or 10	LPT MRK08
Mix 09	9p in Green, 9q in Orange, 17q in Orange and Green (Yellow), D17Z1 in Blue	5 or 10	LPT MRK09
Mix 10	10p in Green, 10q in Orange, 15q in Orange and Green (Yellow), PML (15q24) in Blue	5 or 10	LPT MRK10
Mix 11	11p in Green, 11q in Orange, 18p in Orange and Green (Yellow), D18Z1 in Blue	5 or 10	LPT MRK11
Mix 12	12p in Green, 12q in Orange, 18q in Orange and Green (Yellow), D18Z1 in Blue	5 or 10	LPT MRK12
Mix 13	16p in Green, 16q in Orange	5 or 10	LPT MRK13
Mix 14	19p in Green, 19q in Orange, E2A (TCF3) (19p13) in Blue	5 or 10	LPT MRK14
Mix 15	20p in Green, 20q in Orange	5 or 10	LPT MRK15

*for 5 test kit, add -S to catalogue number, e.g: LPT MRK##-S



Custom FISH Probes

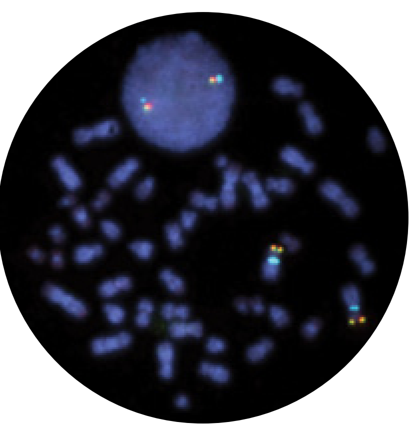
myProbes® Custom FISH Probes



Custom FISH Probes designed to your specifications

RUO

myProbes® is a custom design and manufacture service that provides unique fluorescence *in situ* hybridisation (FISH) probes using the BAC-2-FISH™ process. This process utilises Cytocell's proprietary BAC clone collection containing >220,000 clones to produce fully quality-assured custom FISH probes for virtually any sequence in the entire human genome. Over 2,000 myProbes projects have been completed since 2010.



Based on your specific interests and research, custom FISH probes may range from a simple catalogue probe modification to a truly unique product.

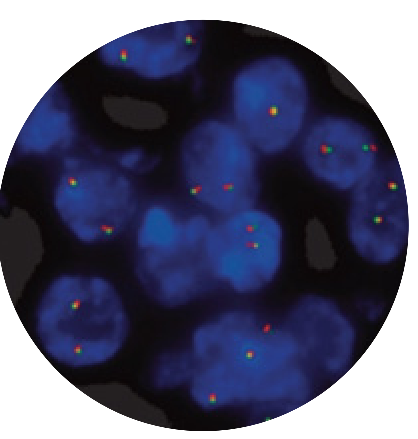
Cytocell offers expert consultation from start to finish on your project. Contact us to learn more.

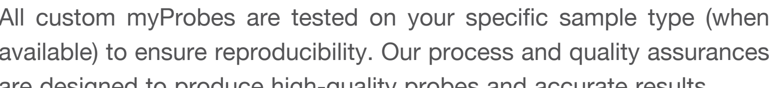
Step 1. Select the gene/target of interest

Step 2. Specify the sample type(s)

Step 3. Specify the probe strategy required

Step 4. Choose the colour

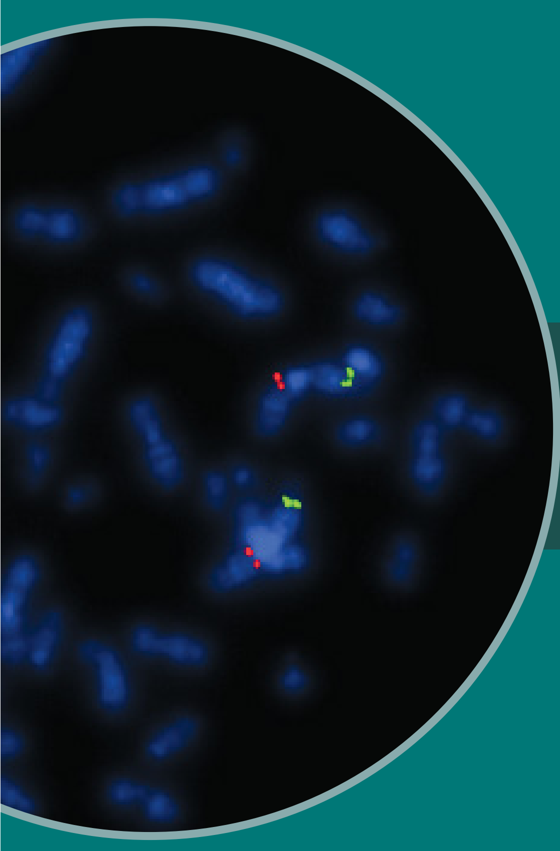




All custom myProbes are tested on your specific sample type (when available) to ensure reproducibility. Our process and quality assurances are designed to produce high-quality probes and accurate results.

A selection of previously manufactured custom probes are searchable online: **www.cytocell.com/custom-search**

For Research Use Only. Not for use in diagnostic procedures. Custom probes are specifically developed for individual customers' RESEARCH USE ONLY (RUO) requirements and not with the intention of being used for in vitro diagnostic examination. Therefore, prior to any future ordering of these probes, users should review the design of such probes to confirm they are suitable for their requirements.



FISH Accessories

FISH Accessories and Ancillary Items

From filters, slides and counterstains to hybridization solutions and chambers, OGT offers a comprehensive range of accessories and ancillary items to support FISH.

Accessories

Cat. No.	Description	Unit Size
PCN009	Porcelain Wash Jars - 12 slide capacity	2
PCN004	Hybridisation Chamber	1
PCN007	24 Square Template Slides	100
PCN008	8 Square Template Slides	100
PCN002	Slide Surface Thermometer	1

Ancillary Reagents

Cat. No.	Description	Unit Size
DES500L	0.125µg/ml DAPI	500µl
DES1000L	0.125µg/ml DAPI	1000µl
DFS500L	1.0µg/ml DAPI	500µl
DSS500L	0.0625µg/ml DAPI	500µl
HB500L	Hybridisation Solution B	500µl
HB1000L	Hybridisation Solution B	1000µl
LPS100	Aquarius® Tissue Pretreatment Kit*	Reagent 1 (1x1L)
		Reagent 2 (1x10ml)
PCA003	20x SSC	100ml
PCA005	Rubber Solution Glue	15g
PCN003	Mounting Medium	10ml

* LPS100 is provided under agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostics or life science use only

Microscope Filters*

Cat. No.	Description	Unit Size
CF69008	Chroma® Filter: 69008 ET-Aqua/FITC/Texas Red Triple Filter Set	1
CF69011	Chroma® Filter: 69011 ET-Aqua/Green/Orange Triple Filter Set	1
CF49000	Chroma® Filter: 49000 ET-DAPI Single Filter	1
CF49302	Chroma® Filter: 49302 ET-Aqua Single Filter	1
CF49303	Chroma® Filter: 49303 ET-Green Single Filter	1
CF49306	Chroma® Filter: 49306 ET-Red Single Filter	1
CF59010	Chroma® Filter: 59010 ET-Green/Red Dual Filter	1
CF59011	Chroma® Filter: 59011 ET-Green/Orange Dual Filter	1
CF59022	Chroma® Filter: 59022 ET-FITC/Texas Red Dual Filter	1

Blocks

Cat. No.	Description	Unit Size
CBZ0001	Chroma® Block: Zeiss Microscope	1
CBBX051	Chroma® Block: Olympus BX51	1
CBBX061	Chroma® Block: Olympus BX61	1
CBNK050	Chroma® Block: Nikon 50i	1
CBDM550	Chroma® Block: Leica DM5500	1

* Microscope filters are available on request. These filters can be ordered with or without a filter cube.

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Ordering Guide

Recommended products are available from OGT.

Sample and slide preparation

- Tissue Pretreatment Kit * (Cat. No. LPS 100)
- Template slides (Cat. No. PCN 007/008)

Pre-denaturation

- Slide surface thermometer (Cat. No. PCN 002)
- Rubber solution glue (Cat. No. PCA 005)

Denaturation

- Slide surface thermometer (Cat. No. PCN 002)

Hybridisation

- Hybridisation solution (Cat. No. HB 500L/1000L)
- Hybridisation chamber (Cat. No. PCN 004)

Post-hybridisation washes

- Porcelain Wash Jars (Cat. No. PCN 009)
- SCC buffer (Cat. No. PCA 003)
- DAPI (Cat. No. DES 500L/1000L)
- Mounting medium (Cat. No. PCN 003)

Analyze

- Filter block (Cat. No. CBZ 001, CBBX 051, CBBX 061, CBNK 050 or CBDM 550)
- Filter (Cat. No. CF 69008/69011/49000, 49302, 49303/49306/59010/59011/59022)

*This product is provided under agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostics or life science use only. See page 93 for product information.

SureSeq™ NGS Products for Haematology and Solid Tumour Cancers

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RUO

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SureSeq

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Overview

The application of next generation sequencing (NGS) technologies to cancer research in recent years has provided novel insights into disease initiation, progression and response to therapy. This powerful technique allows for accurate analysis of nucleotide-level aberrations such as single nucleotide variants (SNVs), insertions and deletions (indels) and structural aberrations including copy-number variations (CNVs) and translocations.

SureSeq™ NGS products include targeted panels and library preparation products for the accurate detection of a wide range of somatic variants and structural aberrations, using a streamlined NGS workflow.

Utilizing hybridisation-based enrichment, SureSeq NGS cancer panels deliver unparalleled coverage uniformity, excellent run-to-run consistency and ensure highly reproducible data. These factors are particularly important when studying heterogeneous cancer samples, where the ability to detect mutations with low minor allele frequency (MAF) at high accuracy is required. More so, facilitated by OGT's excellent bait design and software, structural aberrations including CNVs, loss-of-heterozygosity (LOH) and translocations can easily be identified.

SureSeq NGS products include pre-designed panels for specific disease groups, as well as an expanded library of pre-optimised custom cancer panel content that allows researchers to create NGS cancer panels meeting their exact requirements.

For more information, visit **www.ogt.com/ngs_products**

RUO: For research use only. Not for use in diagnostic procedures.

SureSeq myPanel™ NGS Custom Cancer Panels

Simply mix and match the genes, exonic or intronic content you need to create an NGS cancer panel that meets your exact requirements.

SureSeq myPanel offers:

- Hybridisation-based panel delivering unparalleled coverage uniformity — Detect low frequency variants consistently with confidence and minimize the requirement for supplementary fill-in with Sanger sequencing
- Pre-optimised panels that meet your technical requirements and work with your samples (including FFPE tissue) — No more laborious in-house optimisation, decreasing assay development time
- Bespoke panel content — Sequence only what's relevant for your cancer research, increase throughput and save on sequencing reagents
- Panel content designed with experts and from current literature to target all relevant regions including intronic and splice sites — Get the most comprehensive insight into disease-driving mutations

SureSeq myPanel pre-optimised NGS custom panel content is available for research into a wide range of conditions, including:

Haematology Panels	Solid Tumour Panels
Acute Myeloid Leukaemia	Bladder Cancer
Chronic Lymphocytic Leukaemia	Breast Cancer
Chronic Myeloid Leukaemia	Colorectal Cancer
Multiple Myeloma	Glioma
Myelodysplastic Syndromes (MDS)	Lung Cancer
Myeloid Disorders	Melanoma
Myeloproliferative neoplasms (MPN)/ Myelodysplastic syndromes (MDS) Overlap	Ovarian Cancer
	Prostate Cancer
	Sarcoma

Put our expertise to work for you

Go to www.ogt.com/ngs_products to find out more about SureSeq NGS Custom Cancer Panels, library preparation kits, reagents and Interpret, our complimentary, easy-to-use next generation sequencing analysis solution.

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Getting started with your next SureSeq myPanel NGS Custom Cancer panel could not be simpler

SELECT
Select the gene / exon / intron content you need from OGT's regularly updated, expert curated content library

PREPARE
OGT prepares a fully pre-optimised panel to your specification

VALIDATE
You validate the performance of the panel in your laboratory workflow

APPROVE
Following approval, OGT ships the final panel to you

EXPERIENCE
You experience the superior performance of a SureSeq NGS Custom Panel

CHANGE
New discoveries drive a change in your research workflow

SureSeq myPanel
It really is this quick and easy…

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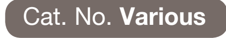

SureSeq myPanel NGS Custom AML Panel

Acute myeloid leukaemia (AML) is the most common type of acute leukaemia in adults. Our understanding of AML has been transformed in recent years to a disease classified largely based on genetic, genomic and molecular characteristics. Key genes implicated in AML progression include *CEBPA, NPM1, FLT3* and *KMT2A (MLL)* with mutations in multiple additional genes identified in recent research[1].

Choose your perfect AML NGS panel from our range of fully tested and optimised panel content. Simply mix and match the genes or individual exons you require for your research and get the most out of your sequencing runs.

SureSeq myPanel Custom AML Panels offer:

- Unparalleled coverage uniformity across all content including *CEBPA* — confidently detect AML variants and remove the requirement for supplementary fill-in approaches
- Bespoke panels with pre-optimised content — create your ideal AML panel and sequence only what's relevant for your AML research
- Robust detection of *FLT3*-ITDs and *KMT2A*-PTDs — streamline your laboratory workflow with a single NGS assay for comprehensive aberration detection in AML
- Complimentary Interpret data analysis software — easy-to-use analysis solution for accurate detection of all variants

Select from any of the following myPanel AML gene or exonic content:

ASXL1	*BCOR*	*BCORL1*	*CBLB*	*CBLC*	*CEBPA*
CUX1	*DDX41*	*DNMT3A*	*ETV6*	*FLT3*	*GATA1*
IDH1	*IDH2*	*IKZF1*	*IRF1*	*JAK3*	*KIT*
KMT2A	*KRAS*	*NPM1*	*NRAS*	*PHF6*	*RUNX1*
SMC1A	*TET2*	*TP53*	*U2AF1*	*WT1*	

REFERENCES

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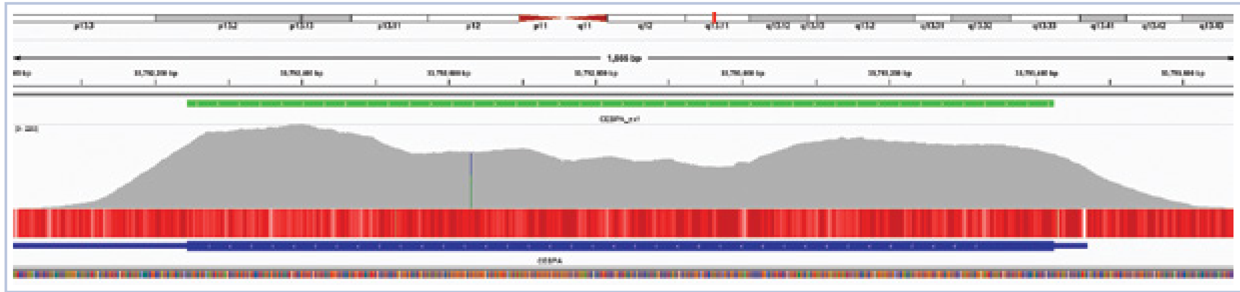

Figure 1: Illustration of the excellent coverage uniformity of the *CEBPA* gene. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

Figure 2: Facilitated by OGT's expert bait design, *FLT3*-ITDs of various sizes and even regions containing multiple ITDs can be confidently detected. ITD sizes are **A** 174 bp, **B** 225 bp, **C** 195 bp with additional 6 bp, **D** 120 bp and **E** 168 bp with additional 69 bp.

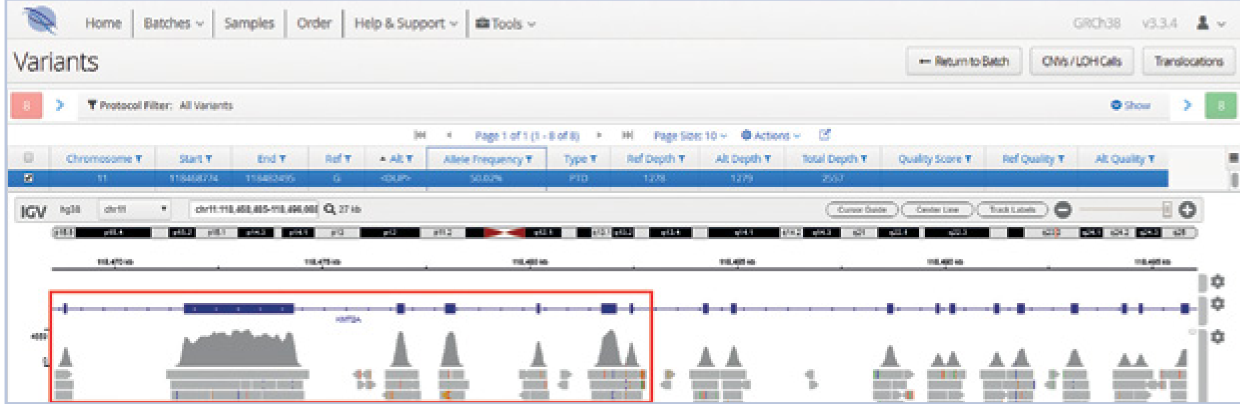

Figure 3: PTD detected spanning exons 2-8 of *KMT2A* by OGT's Interpret NGS analysis software.

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SureSeq myPanel NGS Custom Breast Cancer Panel

Breast cancer is the most common cancer in women after skin cancer. Approximately one out of eight women will be diagnosed in their lifetime with some form of breast cancer. Next generation sequencing (NGS) has enabled the simultaneous study of mutations in high-penetrance breast cancer predisposition genes. These include *BRCA1*, *BRCA2* and other high-risk breast cancer susceptibility genes such as *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden's syndrome) and *PIK3CA*, as well as more moderate-risk genes such as *PALB2*, *BRIP1, RAD51C* and *RAD51D*.

Superior Coverage Uniformity

Mutations in *BRCA1* and *BRCA2* genes lead to an increased susceptibility to breast, ovarian, and other cancers. Figure1a, illustrates the superior uniformity of coverage of key exons of *BRCA1*, and Figure 1b, *BRCA2* from an FFPE sample with SureSeq compared to an amplicon-based panel.

Key Genomic Regions Covered

The *PI3K* pathway is the most frequently enhanced oncogenic pathway in breast cancer. Among mechanisms of *PI3K* enhancement, *PIK3CA* mutations are most frequently (~30%) observed, with the majority of *PIK3CA* somatic mutations located in two "hot spots": E542K or E545K in exon 9, and H1047R or H1047L in exon 20[1], figures 2a and 2b.

GC-rich regions: handled with ease

Sequencing of another frequently mutated breast cancer gene, *TP53*, where point mutations are predominantly located in exons 5-8[2], is often hampered by the GC-rich content, which can lead to technical challenges in assay design and analysis. OGT's innovative bait design overcomes this issue, offering a high level of uniform coverage for these difficult genes to sequence in FFPE samples (Figure 3).

Choose your ideal breast cancer NGS panel from our range of fully tested and optimised NGS panel content. Simply mix and match the genes or individual exons you require and get the most out of your sequencing runs. Use in conjunction with the SureSeq FFPE DNA Repair Mix* for improved NGS library yields, %OTR and mean target coverage from challenging FFPE derived samples.

Select from any of the following myPanel breast cancer whole gene or exonic content below:

APC	*BRCA2*	*CHEK2*	*GATA3*	*PIK3CA*
RB1	*ATM*	*BRIP1*	*EGFR*	*MSH6*
PTEN	*SF3B1*	*BARD1*	*CDH1*	*ERBB2*
NBN	*RAD51C*	*STK11*	*BRCA1*	*CDK12*
ESR1	*PALB2*	*RAD51D*	*TP53*	

REFERENCES

1. Mukohara, Breast Cancer (Dove Med Press). 2015; 7: 111–123.
2. Langerød et al, Clin Cancer Res; 2013; 3569–80

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

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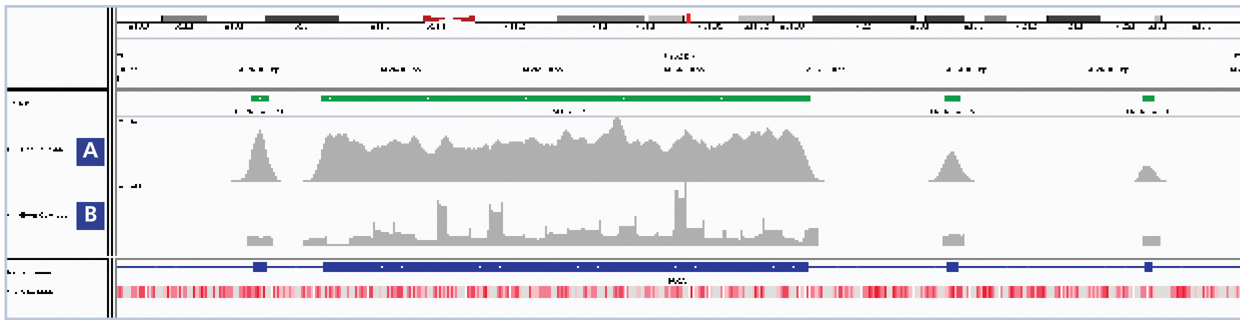

Figure 1: *BRCA1* exons 8, 9, 10 and 11 coverage, Figure 1b: *BRCA2* exons 11, 12 and 13. **A** SureSeq, **B** Amplicon panel. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

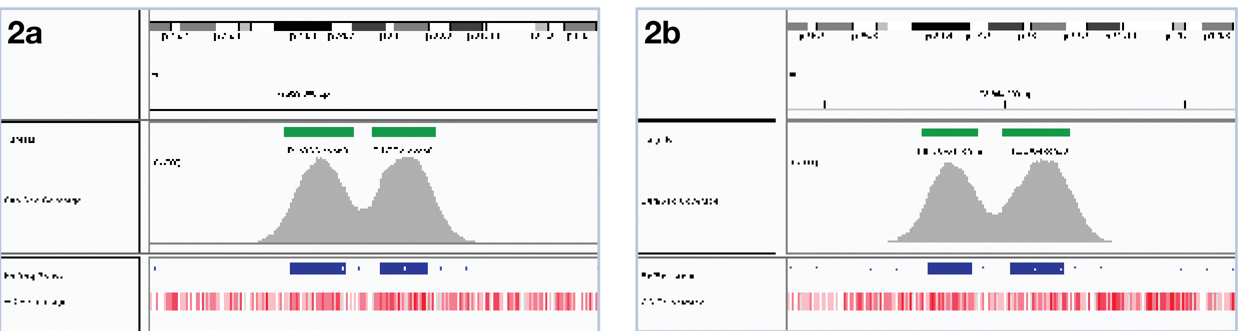

Figure 2a and 2b: Illustration of the excellent uniformity of coverage of *PIK3CA* exons 9 (2a) and 20 (2b). Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

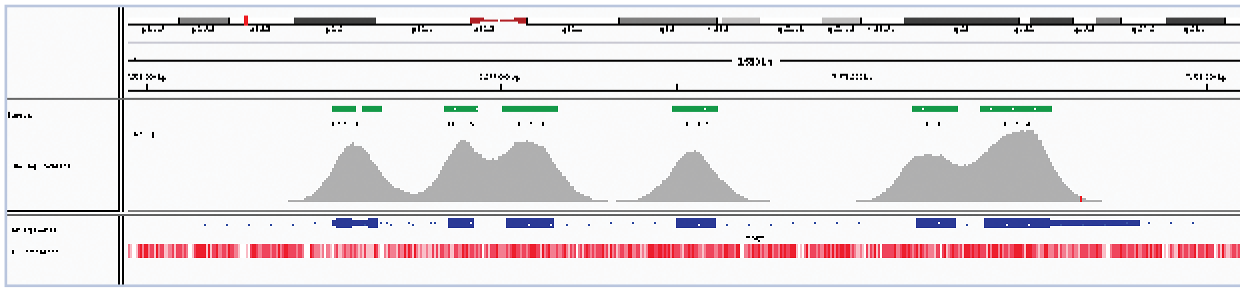

Figure 3: *TP53* exons 3 – 9, exceptional uniformity of coverage in spite of the high GC content of the region. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

For information on the SureSeq FFPE DNA Repair Mix, see page 185.*

SureSeq myPanel NGS Custom Colorectal Cancer Panel

Colorectal cancer (CRC) is the third most common cancer in men (746,000 cases,10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide[1]. Next generation sequencing (NGS) has enabled the simultaneous study of mutations in high-penetrance colorectal cancer genes. These include *KRAS*, *APC* and *TP53* as well as more moderate-risk genes such as *ERBB2*, *PTEN* and *BRAF*.[2]

Superior Coverage Uniformity

KRAS mutations are found in approximately 35-45% of colorectal cancers with around 80% occurring in codon 12 and 15% in codon 13 of exon 2; other commonly reported mutations are found in exons 3 and 4[3]. The tumour suppressor gene *APC* plays an important role in CRC development. Absence of the *APC* protein leads to accumulation of beta-catenin in the cytoplasm, which may contribute to tumour progression. 60% of all somatic mutations in *APC* occur within the mutation cluster region between codons 1286 and 1513 on exon 15[4]. Figures 1a, b, c and 2 illustrate the superior uniformity of coverage of these key genomic regions.

Approximately 8-15% of colorectal cancers involve mutations in the *BRAF* gene, with up to 90% of these a result of a mutation at V600E, located on exon 15[5]. In *TP53*, another frequently mutated cancer gene, point mutations are predominantly located in exons 5-8[2], however sequencing is often hampered by the GC-rich content, which can lead to technical challenges in assay design and analysis. OGT's innovative bait design overcomes this issue, offering a high level of uniform coverage for these difficult genes to sequence in FFPE samples, Figure 4.

Choose your ideal colorectal cancer NGS panel from our range of fully tested and optimised NGS panel content. Simply mix and match the genes or individual exons you require and get the most out of your sequencing runs. Use in conjunction with the SureSeq FFPE DNA Repair Mix* for improved NGS library yields, %OTR and mean target coverage from challenging FFPE derived samples.

Select from any of the following myPanel colorectal whole gene or exonic content below:

APC	*CDH1*	*ERBB2*	*KRAS*	*MSH6*	*PIK3CA*	*STK11*
BRAF	*CHEK2*	*HRAS*	*MET*	*NRAS*	*PTEN*	*TP53*

REFERENCES

1. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2. Han et al, PLoS One. 2013; 8(5): e64271
3. Tan et al, World J Gastroenterol. 2012 Oct 7; 18(37): 5171–51804
4. More, et al, Hum Mol Genet (1992) 1 (4): 229-233
5. https://www.mycancergenome.org/content/disease/colorectal-cancer/braf/54/

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

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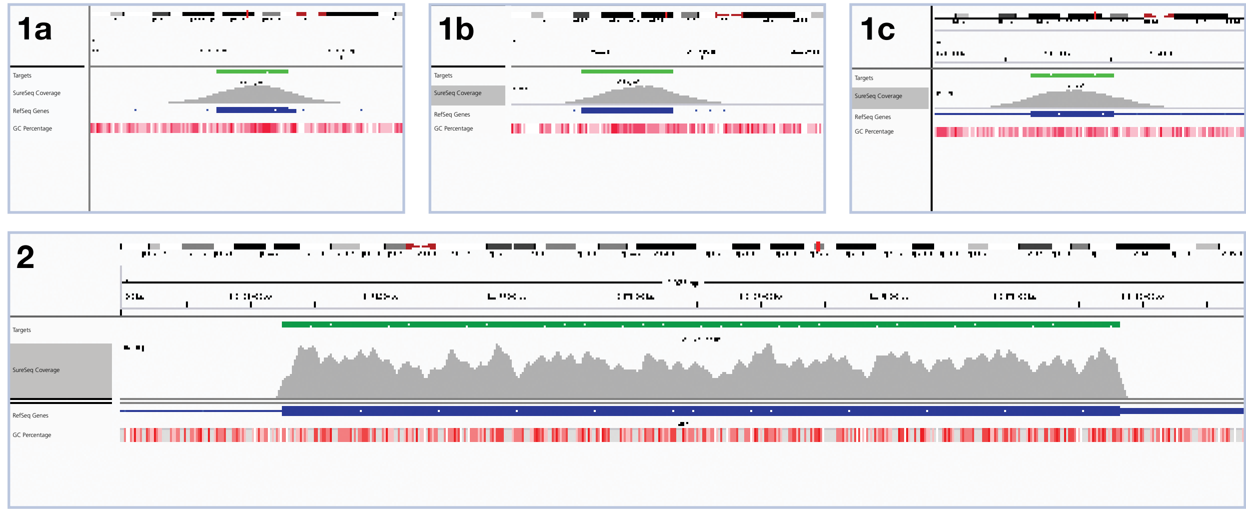
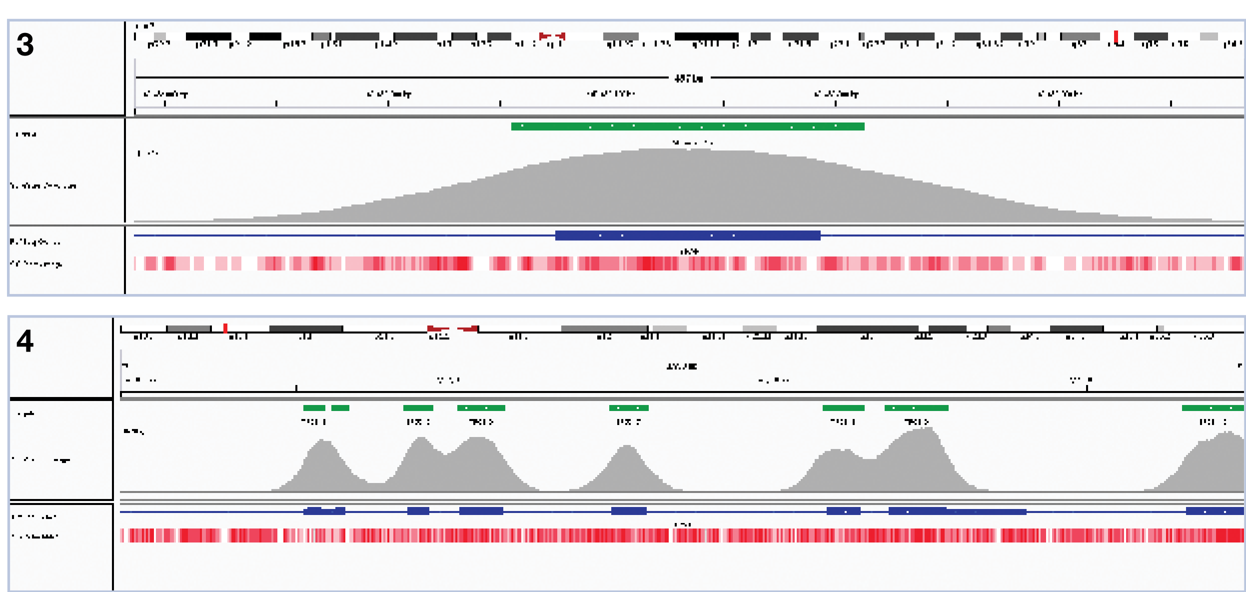


Figure 1a, b, c: *KRAS* exons 2, 3 and 4 coverage.
Figure 2: *APC* exon 15 coverage. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).



Figures 3 and 4: Illustration of the excellent uniformity of coverage of (Figure 3) *BRAF* exon 15 and *TP53* exons 3 - 9 (Figure 4). Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

For information on the SureSeq FFPE DNA Repair Mix, see page 185.*

SureSeq myPanel NGS Custom Melanoma Cancer Panel

Cutaneous melanoma (CM) is the most dangerous form of skin tumour and causes 90% of skin cancer mortality[1]. With recurrent somatic mutations in *BRAF*, *NRAS*, *KIT* and *NF1* among the most common genetic aberrations underlying pathogenesis of melanoma, next generation sequencing (NGS) has been an invaluable tool in helping to characterize the overall genomic landscape of melanomas.

Superior Coverage Uniformity

The most frequently activated pathway in melanoma is the mitogen-activated protein kinase (MAPK) pathway, often activated through mutations in the V600 codon of BRAF (in 35–50% of melanomas) and the Q61 codon of *NRAS* (10–25%)[2], with mutations being mutually exclusive.

Mutations of *KIT* are found in particular subsets of melanoma, where the mutations activate signal-transduction pathways (MAPK and PI3K) that ultimately lead to cell proliferation. Approximately 70% of *KIT* mutations identified in melanoma are found in exon 11, most commonly L576P (Figure 1a and 1b).

Neurofibromatosis type 1 (*NF1*) is a relatively common tumour predisposition syndrome related to germline aberrations of *NF1*, a tumour suppressor gene. Recent studies have additionally shown *NF1* to play a critical role in somatic events in a wide range of tumours, including melanoma. The tumour suppressor function of neurofibromin is largely attributed to a small central region which comprises 360 amino acids encoded by exons 20-27a[3]. OGT's expert bait design offers excellent uniformity for all of these key genes associated with melanoma (Figure 1).

Choose your ideal melanoma NGS panel from our range of fully tested and optimised NGS panel content. Simply mix and match the genes or individual exons you require and get the most out of your sequencing runs. Use in conjunction with the SureSeq FFPE DNA Repair Mix* for improved NGS library yields, %OTR and mean target coverage from challenging FFPE derived samples.

Select from any of the following myPanel melanoma whole gene or exonic content below:

BRAF	*KIT*	*NF1***	*NRAS*

REFERENCES

1. Garbe *et al*, European Journal of Cancer 63 (2016) 201-217
2. Tsao *et al*, Genes & Dev. 2012. 26: 1131-1155
3. Yap *et al*, Oncotarget, 2014, Vol. 5, No. 15

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

**Due to the presence of pseudogenes in NF1, it is recommended that an orthogonal technique is used to verify any mutations detected.

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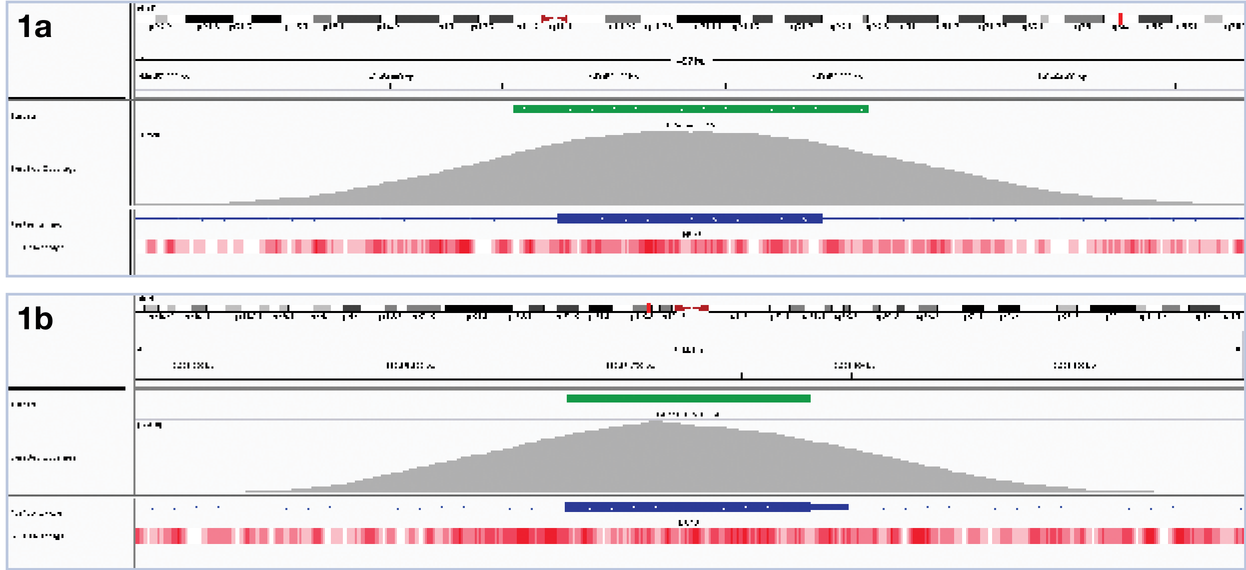

Figure 1: Illustration of the exceptional uniformity of coverage of *BRAF* exon 15 (1a), *NRAS* exon 2 (1b) with a SureSeq melanoma panel. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

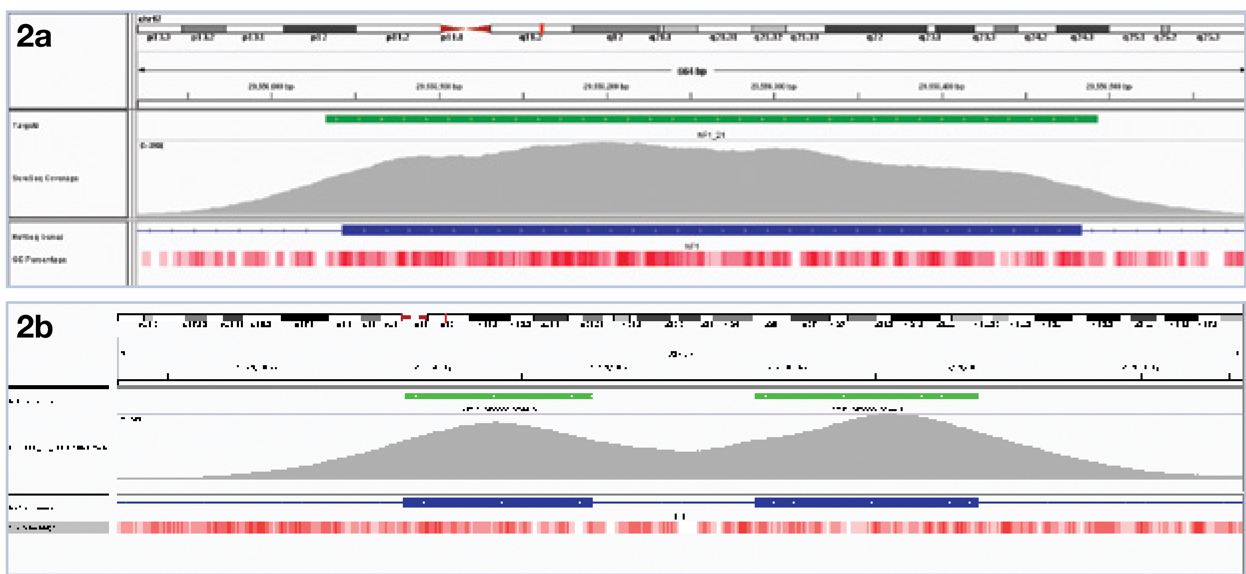

Figure 2: Even coverage of *NF1* exon 21 (2a) and *KIT* exons 10 and 11 (2b) with a SureSeq melanoma panel. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

For information on the SureSeq FFPE DNA Repair Mix, see page 185.*

SureSeq myPanel NGS Custom Prostate Cancer Panel

Prostate cancer is now the second leading cause of cancer in men, with recent genome-wide studies helping to clarify the genetic basis of this common but complex disease[1]. Many of these studies have reinforced the importance of homologous end repair genes including: *ATM, BRCA1, BRCA2* and *PALB2*, in the mechanism of prostate cancer development. Mutations in these genes result in cells having to repair lesions through other non-conservative mutagenic mechanisms.

Superior Coverage Uniformity

A number of genetic factors have been found that increase prostate cancer risk, including heritable mutations in the genes *BRCA1* and *BRCA2*. *BRCA1* is a key player in cellular control systems, having been linked to DNA damage response and repair, transcriptional regulation and chromatin modelling[2], while *BRCA2* function is linked to DNA recombination and repair processes, being of particular importance in the regulation of *RAD51* activity. Figure 1a, illustrates the superior uniformity of coverage of key exons of *BRCA1*, and Figure 1b, *BRCA2* from an FFPE sample.

PALB2 is a *BRCA2* binding protein and the *BRCA2-PALB2* interaction is essential for *BRCA2*-mediated DNA repair. Recently it has been shown that correct *PALB2* function is necessary for the homologous recombination repair via interaction with *BRCA1*, revealing that *PALB2* is actually a linker between *BRCA1* and *BRCA2*[3]. Figures 2 illustrate the excellent uniformity of coverage of key exons of *PALB2*.

Choose your ideal prostate cancer NGS panel from our range of fully optimised NGS panel content. Simply mix and match the genes or individual exons you require and get the most out of your sequencing runs. Use in conjunction with the SureSeq FFPE DNA Repair Mix* for improved NGS library yields, %OTR (on target rate) and mean target coverage from challenging FFPE derived samples.

Select from any of the following myPanel Prostate Cancer whole gene or exonic content below:

ATM	*BRCA1*	*BRCA2*	*PALB2*

REFERENCES

1. Thoma, C, (2015) The complex relationships of malignant cells in lethal metastatic castration-resistant disease, Nature Reviews Urology 12, 237
2. Castro, E. *et al*, (2012) The role of BRCA1 and BRCA2 in prostate cancer. Asian Journal of Andrology, 14 (3):409-414.
3. Pakkanen, S. *et al*, (2009) PALB2 variants in hereditary and unselected Finnish Prostate cancer cases. Journal of Negative Results in BioMedicine, 8 (1).

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

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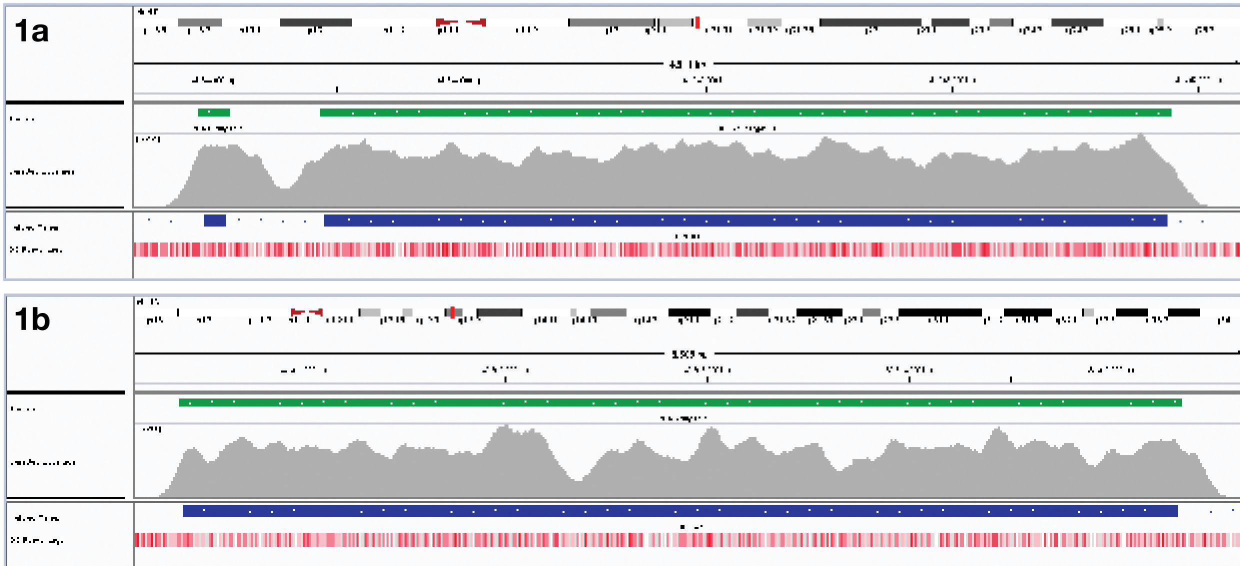
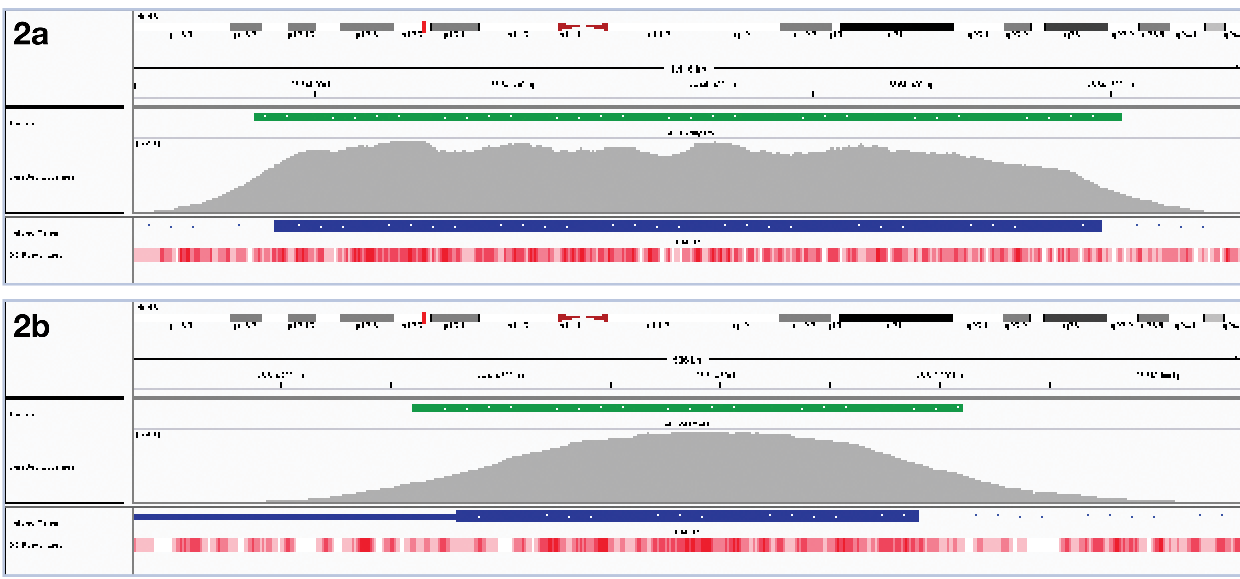


Figure 1a: *BRCA1* exon 9 and 10 coverage, **Figure 1b**. *BRCA2* exon 11 coverage. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).



Figures 2a and 2b: Illustration of the excellent uniformity of coverage of *PALB2* exons 5 (2a) and 13 (2b). Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red).

For information on the SureSeq FFPE DNA Repair Mix, see page 185.*

Cat. No. **602022-16** (16 reactions)
Cat. No. **602022-96** (96 reactions)

SureSeq CLL + CNV Panel

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in adults. A wide variety of chromosomal abnormalities are associated with CLL, ranging from single nucleotide variants (SNVs) and insertions/deletions (indels) up to large copy-number variations (CNVs), including trisomies.

The SureSeq CLL + CNV Panel has been designed in collaboration with recognised cancer experts to detect 12 key genes and 5 chromosomal regions implicated in CLL progression (Table 1). The SureSeq CLL + CNV Panel alleviates the burden of running multiple assays and streamlines your CLL research to deliver a comprehensive genomic profile for each CLL sample using a single workflow.

The SureSeq CLL + CNV Panel offers:

- Unparalleled uniformity and high depth of coverage — detect low-frequency SNVs and indels with confidence
- CNV detection ranging from loss of single exons to full chromosome arms and trisomy 12 — profile your samples for CNVs in the 5 most commonly aberrant regions in CLL
- Time savings - replace multiple assays with a single NGS panel, increasing throughput and reducing turnaround time
- Complimentary data analysis software — analyse your data with Interpret data analysis software, OGT's powerful and easy-to-use analysis solution for accurate identification of all variants and CNVs

OGT's expert bait design delivers outstanding uniformity and depth of coverage, offering confident detection of low frequency SNVs and indels down to 1% minor allele frequency (MAF) in 14 genes, including 2 genes and 24 SNPs to allow for easy sample tracking[2]. The SureSeq CLL + CNV Panel covers the 5 most common CNVs in CLL and enables detection down to 10% MAF, corresponding to 20% tumour content. Compared to array data, often considered the gold standard for CNV detection, the events reported with the SureSeq CLL + CNV Panel were 100% concordant, even in genomic regions containing multiple aberrations (Figures 1-2). More so, facilitated by OGT's excellent bait design, loss-of-heterozygosity (LOH) can be identified. With CNV detection ranging from loss of single exons to full chromosome arms and trisomy 12, your data provides a more comprehensive genetic picture for each CLL sample from a single assay.

The SureSeq CLL + CNV Panel comes with OGT's complimentary data analysis software, Interpret. Designed to work seamlessly with all SureSeq panels, Interpret delivers fast and accurate detection of all SNVs, indels, LOH and CNVs covered by the panel, for an effortless translation of all your CLL data into meaningful results.

REFERENCES

1. Döhner *et al.*, N Engl J Med 2000;343:1910-1916
2. Pengelly *et al.*, Genome Med 2013;5:89

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The SureSeq CLL + CNV Panel in numbers

Feature	Specification
Number of genes	14
Uniformity Coverage	>99% of bases at >20% of the mean target coverage
Mean target coverage	>1000x
DNA input recommended	>500ng high quality DNA
Gene list **CNV list** **Sample tracking**	*ATM, PLCG2, BIRC3, BRAF, TP53, XPO1, SF3B1, KRAS, MYD88, SAMHD1, NOTCH1* and *BTK* 17p (covering *TP53*), 11q (covering *ATM*),13q (covering *RB1/DLEU2/DLEU7*), 6q (6q23.2-6q23.3 covering *MYB*) and Trisomy 12 *CXCR4* and *SRY* + 24 SNP profiling panel[2]
Limit of Detection	SNVs/indels: MAF of 1% within the 14 genes CNVs: MAF of 10% within the 5 chromosomal regions
CNV detection size	11q: - single exon to whole gene of ATM - > 5-10 Mb for the rest of the 11q arm 17p: - single exon to whole gene of TP53 - > 5-10 Mb for the rest of the 17p arm 13q: - del(13)(q14) type I (short) and del(13q)(q14) type II (larger) events covering *RB1/DLEU2/DLEU7* - > 10-20 Mb for the rest of the 13q arm 6q (6q23.2-6q23.3): - single exon to whole gene of *MYB* plus 1MB flanking sequence on either side Trisomy 12: - whole chromosome
LOH detection size	11q and 17p: 5-10 Mb 13q: 10-20 Mb
Samples per MiSeq® v2 run	16 samples/ run

Table 1: The SureSeq CLL + CNV Panel targets the 5 most common chromosomal regions implicated in CLL and 14 genes, including 2 genes and 24 SNPs for easy sample tracking[2].

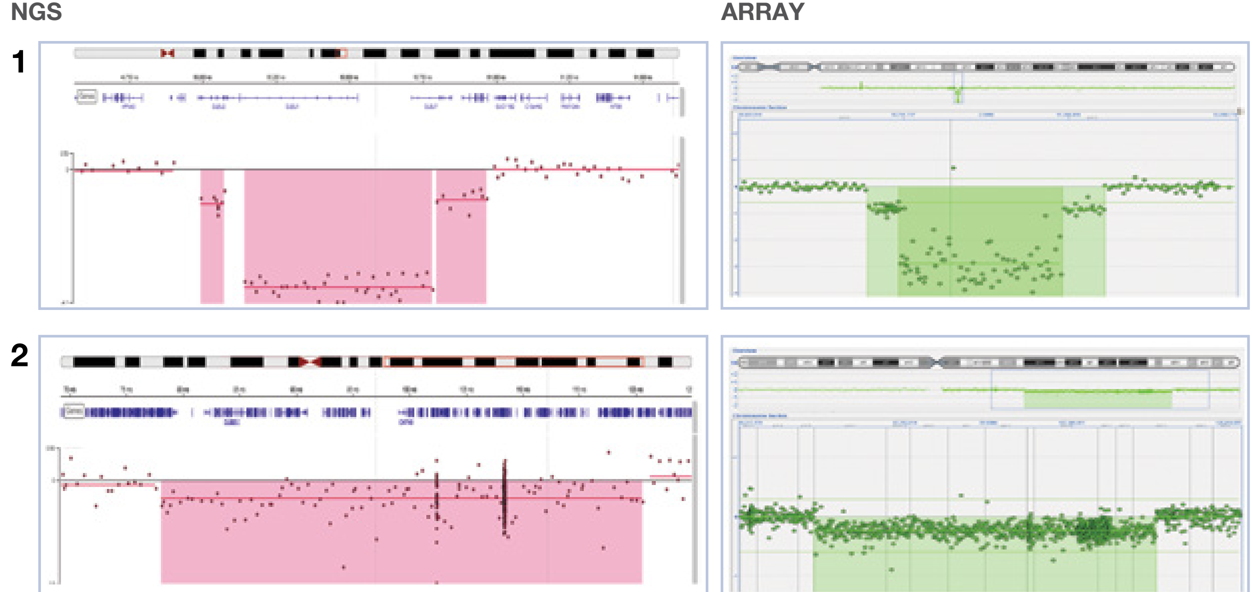

Figure 1: 0.6Mb biallelic loss called within a larger ~1Mb single allele deletion in the region covering *DLEU2/DLEU1/DLEU7* on chromosome 13q.
Figure 2: 42.7Mb deletion of 11q covering *ATM*.

Cat. No. **602022** (16 reactions)
Cat. No. **602001** (96 reactions)

SureSeq Core MPN Panel

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of diseases characterised by the overproduction of one or more types of blood cells. The SureSeq Core MPN Panel has been designed in collaboration with recognised cancer experts to detect somatic variants in 3 clinically relevant MPN-associated genes; *JAK2, MPL* and *CALR* (Table 1). The SureSeq Core MPN Panel provides researchers with a single, 1-day NGS workflow for studies into the diagnosis, aetiology and prognosis of MPNs.

The SureSeq Core MPN Panel offers:

- Unparalleled uniformity and high depth of coverage — detect low frequency SNVs and indels with confidence
- Time and cost savings — replace multiple single gene assays with a focused NGS panel
- 1 day from sample to sequencer — streamlined library preparation and rapid 30-minute hybridisation
- Additional *BCR-ABL* fusion gene detection — customize your panel by adding *BCR-ABL* translocation content
- Complimentary Interpret NGS data analysis software — easy-to-use analysis solution for accurate identification of all variants and translocations

The SureSeq Core MPN Panel is able to consistently detect SNVs and indels down to 1% minor allele frequency (MAF), using a streamlined 1-day workflow. Facilitated by OGT's expert bait design, the panel delivers the turn-around time of an amplicon-based protocol with the superior coverage uniformity of a hybridisation-based panel, enabling confident detection of key MPN variants including a 52 bp deletion in *CALR* exon 9 and a 6 bp deletion in *JAK2* exon 12 (Figures 1 and 2).

The Core MPN Panel in numbers

Feature	Specification
Target regions	*JAK2* exons 12 and 14 *CALR* exon 9 *MPL* exon 10
Panel size	1kb
Mean target coverage	>1000x
Coverage uniformity	V617F
DNA input recommended	>500ng high quality DNA
Limit of detection	SNVs / indels: 1% MAF
Workflow	30 minutes hybridisation, 1-day sample-to-sequencer
Samples per MiSeq® v2 run	48 samples / run

Table 1: The SureSeq Core MPN Panel targets 4 exons in 3 genes implicated in MPNs, covering various key MPN driver mutations.

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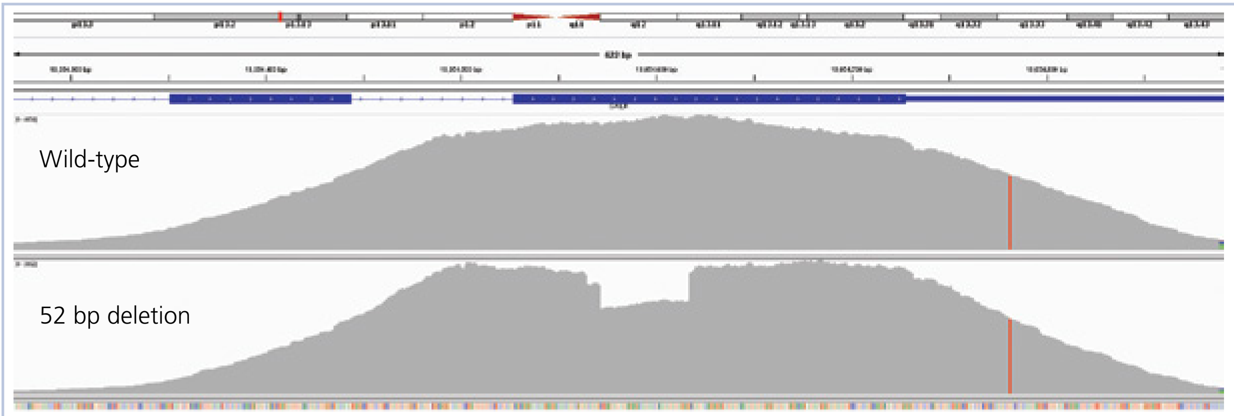

Figure 1: Detection of a 52 bp deletion (type 1) in exon 9 of *CALR* (bottom panel), compared to a wild-type sample (top panel).

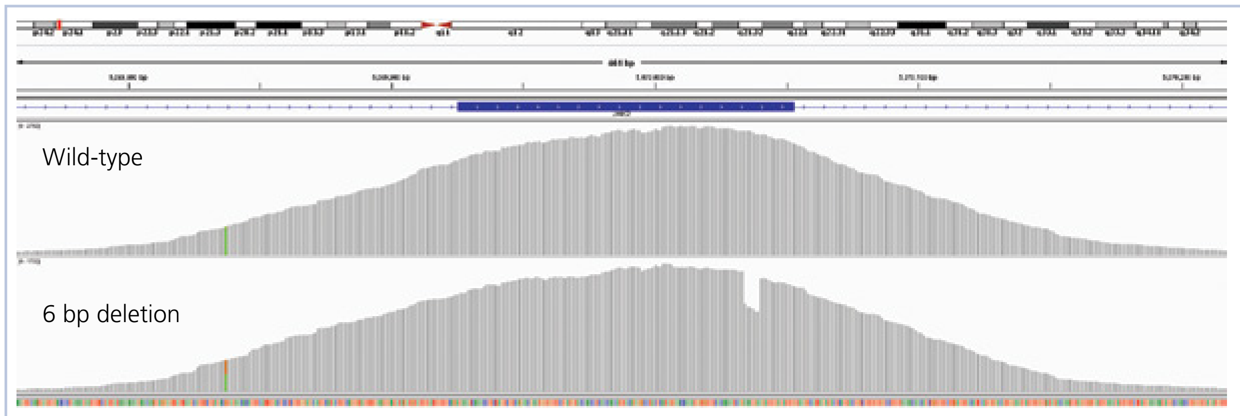

Figure 2: Detection of a 6 bp deletion in exon 12 of *JAK2* (bottom panel), compared to a wild-type sample (top panel).

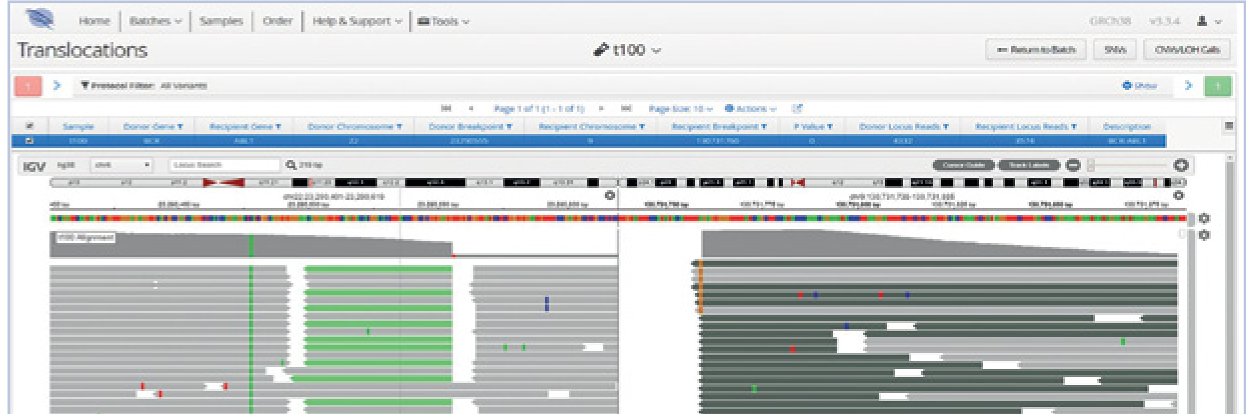

Figure 3: *BCR-ABL* translocation reported in Interpret. Split-reads covering both *BCR* (left panel) and *ABL1* (right panel) are detected, indicative of the *BCR-ABL* gene fusion.

We would like to thank Professor Nick Cross (National Genetics Reference Laboratory - Wessex, UK) for providing the validated research samples and West Midlands Regional Genetic Laboratory, Birmingham, for providing the BCR-ABL samples.

Cat. No. **600073** (16 reactions)
Cat. No. **600074** (96 reactions)

SureSeq Ovarian Cancer Panel

Hybridisation-based NGS panel validated on FFPE samples and whole blood; it allows the analysis of variants associated with ovarian cancer and research into therapeutic response

The SureSeq Ovarian Cancer Panel:

- Contains the latest evidence-based genes involved in ovarian cancer research — gain insight into homologous repair deficiencies and cell cycle dysregulation
- Is validated for research use on FFPE and whole blood — detect germline mutations in DNA derived from blood as well as both germline and somatic mutations in DNA derived from FFPE tissue
- Utilises hybridisation-based enrichment — sensitive and reproducible detection of low-frequency variants, even in heterogeneous cancer samples
- Fast and easy workflow — streamlined library preparation, short 4-hour hybridisation and intuitive software allowing easy variant analysis
- Delivers excellent uniformity of coverage across the whole panel — over 99% of targeted regions are covered to at least 20% of mean target coverage

Ovarian cancer is the leading cause of death from gynecological cancers in the Western world[1]. Next generation sequencing (NGS) is quickly becoming a commonly used tool for analysis of mutations — both single nucleotide variants (SNVs) and insertion/deletions (indels) — in genes associated with ovarian cancer. The SureSeq Ovarian Cancer Panel has been developed with leading cancer experts and covers all coding exons of seven genes (Table 1). The panel allows detection of known and novel variants in tumour suppressor genes as well as genes involved in homologous repair to advance research into ovarian cancer treatment. It has been validated on DNA derived from FFPE tissue and whole blood to allow investigation of both germline and somatic mutations.

Utilising hybridisation-based enrichment, the SureSeq Ovarian Cancer Panel delivers excellent run-to-run consistency and extremely uniform coverage across the whole region of interest (Figure 1) to allow sensitive detection of variants present, even at low minor allele frequency (MAF) (Table 2).

The SureSeq Ovarian Cancer panel is optimised to work with the SureSeq NGS Library Preparation Kit*. For more information, see page 183.

REFERENCES

1. Helleman J. et al. (2006) Molecular profiling of platinum resistant ovarian cancer. Int J Cancer 118(8):1963-71.

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

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BRCA1	BRCA2	TP53	PTEN	ATM	ATR	NF1

Table 1: The SureSeq Ovarian Cancer Panel targets seven genes implicated in ovarian cancer.

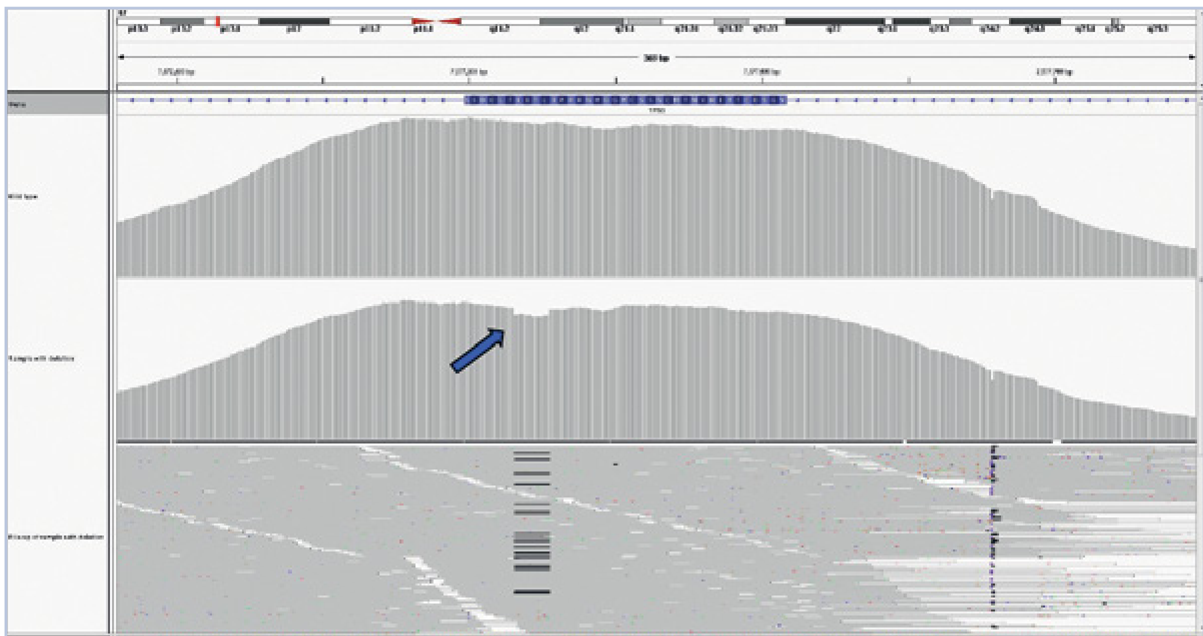

Figure 1: OGT's expert bait design delivers excellent uniformity of coverage. Shown here is FFPE sample, exon 7 of *TP53* (NM_000546). The top panel shows a normal control, the bottom panel shows a deletion (c.754_765delCTCACCATCATC) at 6% frequency. Mean target coverage >1400x, 12 samples per MiSeq lane.

Gene	Variant detected	Type of variant	Mean target coverage	% MAF detected
BRCA1	c.3424G>C (p.Ala1142Pro)	SNV	881	11.92%
BRCA2	c.556G>C (p.Ala186Pro)	SNV	728	1.92%
TP53	c.1129A>C (p.Thr377Pro)	SNV	1024	3.03%
ATR	c.7274G>A (p.Arg2425Gln)	SNV	1579	38.63%
NF1	c.8137_8138insG (p.Phe2714ValfsTer16)	Insertion	683	1.45%
NF1	c.3354delT (p.Ser1118ArgfsTer24)	Deletion	621	1.13%
ATR	c. 4154delC (p.Thr1385MetfsTer3)	Deletion	506	1.61%

Table 2: Example mutations detected in FFPE clinical research samples using the SureSeq Ovarian Cancer Panel. The ability to detect MAFs as low as 1.13% gives added confidence in the variants being called and facilitates the exploration of tumour heterogeneity. Rows 1–4: low-frequency SNVs; rows 5–7: low-frequency indels. Samples kindly provided by Biopathology Department of Gustave Roussy, Villejuif, France.

For information on the SureSeq FFPE DNA Repair Mix, see page 185.*

Cat. No. **600075** (16 reactions)
Cat. No. **600076** (96 reactions)

SureSeq Myeloid Panel

25-gene myeloid disorder hybridisation-based NGS enrichment panel that delivers accurate and easy identification of variants

The SureSeq Myeloid Panel delivers:

- Most up-to-date content designed in collaboration with recognised cancer experts — detect SNVs and indels in 25 genes implicated in a variety of MPNs
- Time and cost saving solution — replace multiple single gene assays with one comprehensive panel
- Sensitive and reproducible variant detection even in heterogeneous samples — detect low-frequency alleles down to 1% MAF with confidence
- Fast and easy workflow — streamlined library preparation, rapid hybridisation and intuitive software allowing easy variant analysis
- Excellent coverage uniformity — 99% of targeted regions are covered to at least 20% of mean target coverage

Myeloproliferative neoplasms (MPNs) are a group of diseases that affect normal blood cell production in the bone marrow resulting in overproduction of one or more cell types (i.e. red cells, white cells or platelets). There are numerous different sub-types of MPNs that are distinguished from each other by the type of cell which is most affected and the genetic profile. The SureSeq Myeloid Panel targets selected key genes known to contain driver mutations for a range of MPNs including polycythaemia vera (PV), essential thrombocythaemia (ET) and myelofibrosis (MF) (Table 1). To obtain the optimal sensitivity whilst maximizing throughput, hot exons where clinically relevant mutations are known, and every exon for tumour suppressor, hereditary and highly implicated research-related genes, are targeted. This allows detection of previously characterised as well as novel variants in myeloid samples.

Instead of assaying for single genes in a sequential manner, the mutational status of twenty-five genes can be rapidly and simultaneously determined with the use of the SureSeq Myeloid Panel.

The SureSeq Myeloid Panel has been validated with samples from the National Institute for Biological Standards and Control (NIBSC) and has been shown to accurately detect alleles down to 1% minor allele frequency (MAF) at a read depth of >1000x.

OGT's expert bait design ensures efficient and more uniform capture of all targeted regions than amplicon-based technologies, so that all variants present can be called with maximum confidence. This has been demonstrated on the *CALR* gene, which is commonly mutated in various MPNs. It is critical to identify key *CALR* indels (types 1 & 2 causing a frameshift) as well as increasingly recognised point mutations in this gene. The SureSeq Myeloid Panel delivers superior performance to panels designed using standard algorithms, by ensuring uniform coverage over the regions of interest (Figure 1).

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ASXL1	EGLN1	IDH2	NRAS	SRSF2
CBL	EPAS1	**JAK2**	RUNX1	TET2
CALR	EPOR	**KIT**	SETBP1	TP53
CSF3R	EZH2	KRAS	SF3B1	U2AF1
DNMT3A	IDH1	**MPL**	SH2B3	VHL

Table 1: The SureSeq Myeloid Panel targets 25 genes implicated in a variety of MPNs. The gene content has been defined with input from recognised cancer experts including Professor Mike Griffiths (West Midlands Regional Genetics Laboratory, UK) and Professor Nick Cross (National Genetics Reference Laboratory – Wessex, UK).

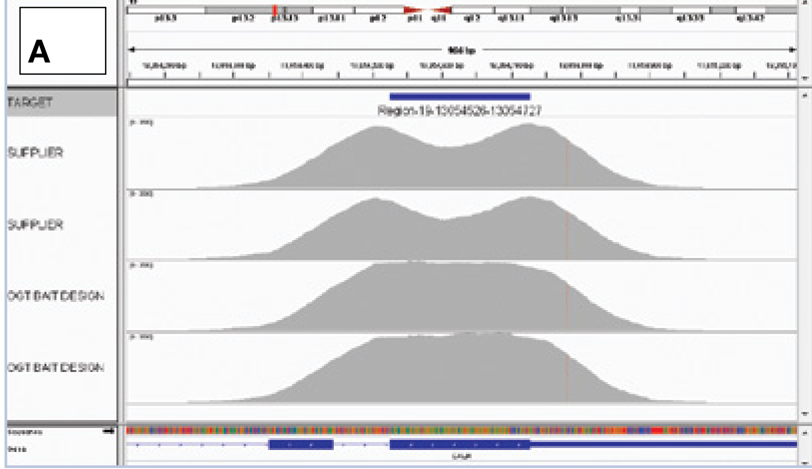
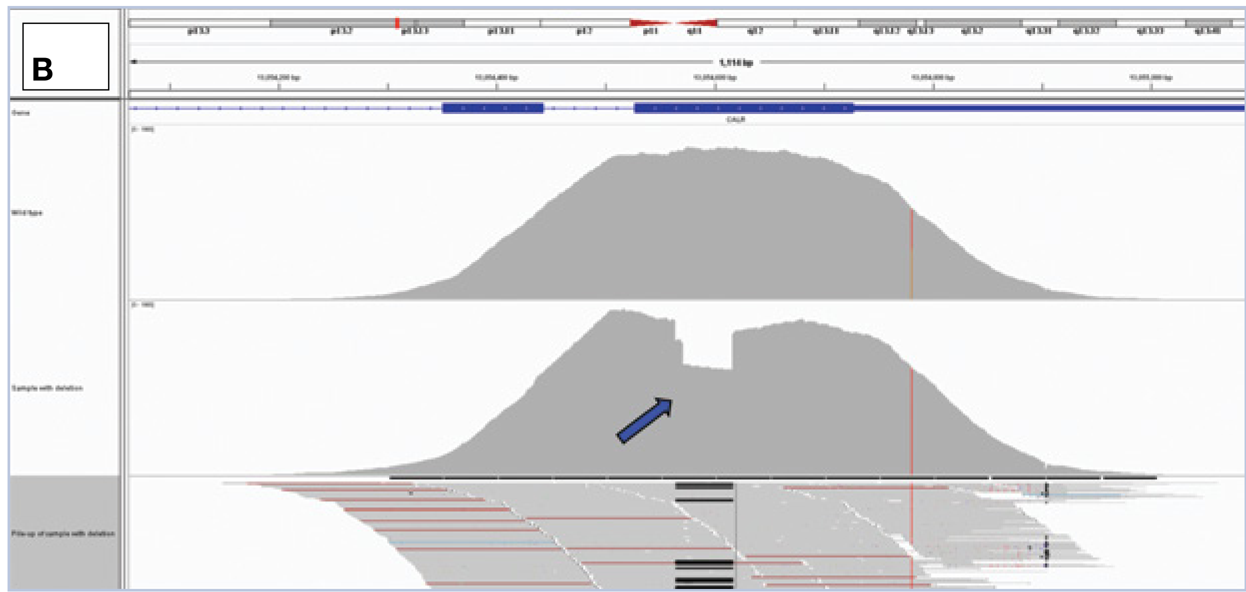


Figure 1: A) OGT's expert bait design delivers improved uniformity of coverage. Shown here is exon 9 of *CALR*. The top two captures have been completed using baits designed with standard commercially available software. They have a considerable dip in coverage in the middle of the exon due to the fact it presents a low complexity region with low nucleotide diversity. Most algorithms would want to avoid such regions in the design. However, OGT's superior bait design can increase the evenness of coverage of such regions. **B)** The top panel shows a normal control sample and the bottom panel shows 23% deletion (c.1092_1143del_52bp) in *CALR* exon 9. Mean target coverage >1000x, 24 samples per MiSeq lane.



Interpret Software

Interpret is a powerful and easy-to-use next generation sequencing analysis solution. Sequencing data can be quickly processed to deliver accurate identification of single nucleotide variants (SNVs) and indels as well as structural variants such as internal and partial tandem duplications (ITDs and PTDs), and copy-number variations (CNVs) including trisomies, loss-of-heterozygosity (LOH) and translocations. Coupled with a comprehensive and powerful filtering framework, the software delivers accurate mutation calling with 100% sensitivity and 99.9% specificity at >1% variant allele frequency (VAF)*.

Interpret is designed to work seamlessly with OGT's extensive range of SureSeq and CytoSure NGS panels and offers flexible accessibility to analyse your data whether through a stand-alone computer, laboratory server or another web enabled device.

Interpret Software offers:

- Extensive customisation options — easily customise variant and batch reports and database links to meet the exact needs of your laboratory
- Comprehensive range of filtering options — standardise your analysis workflow and overlay bespoke variant filtering to meet your analytical criteria
- Security and control — log and track user activity and standardise analysis protocols through multiple access permission levels
- Powerful analysis capability — optimised for use with OGT's NGS panels for confident annotation and reporting of low frequency variants

Used in conjunction with OGT's NGS panels, Interpret compliments the expert panel design and hybridisation-based approach of SureSeq and CytoSure NGS to enable the effortless translation of NGS data into meaningful results.

For more information on Interpret, visit **www.ogt.com/InterpretNGS**.

*Sensitivity and specificity determined using Horizon Discovery OncoSpan and TruQ7 and HapMap (NA12878) standards.

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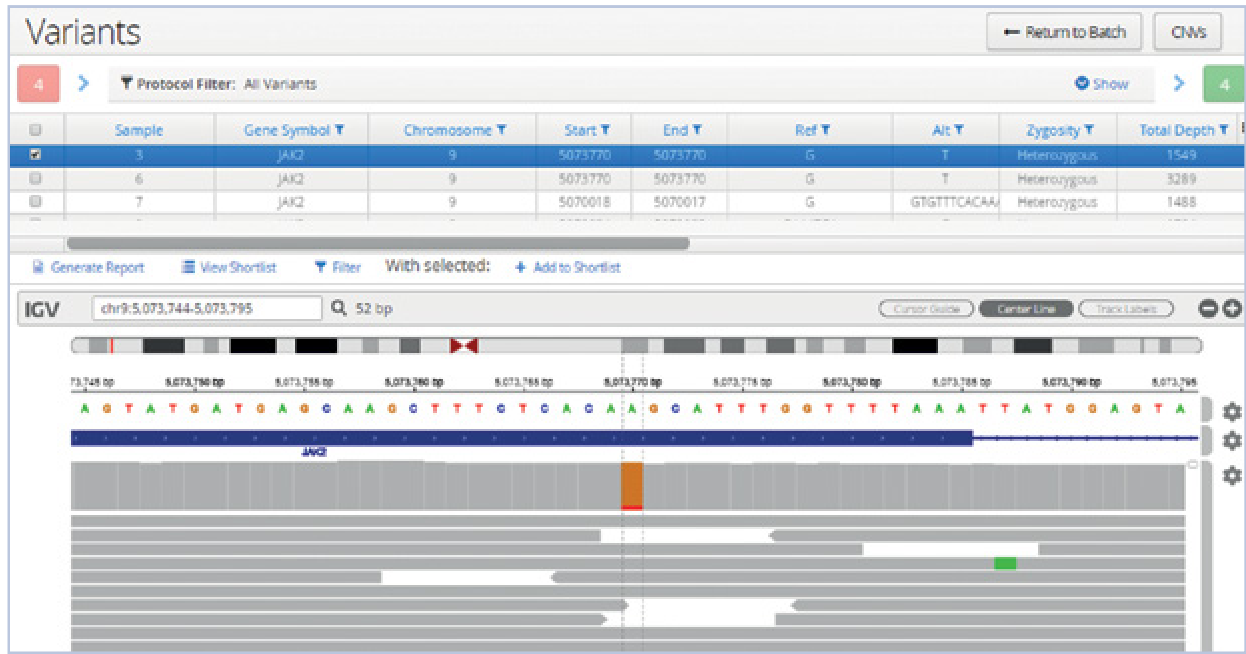


Figure 1: Following analysis, all variants are displayed in a table, below which is an IGV window allowing a more detailed review of the data and additional verification. In this example a low frequency *JAK2* V617F SNV has been selected and the user is able to view the aligned reads generated by the pipeline.

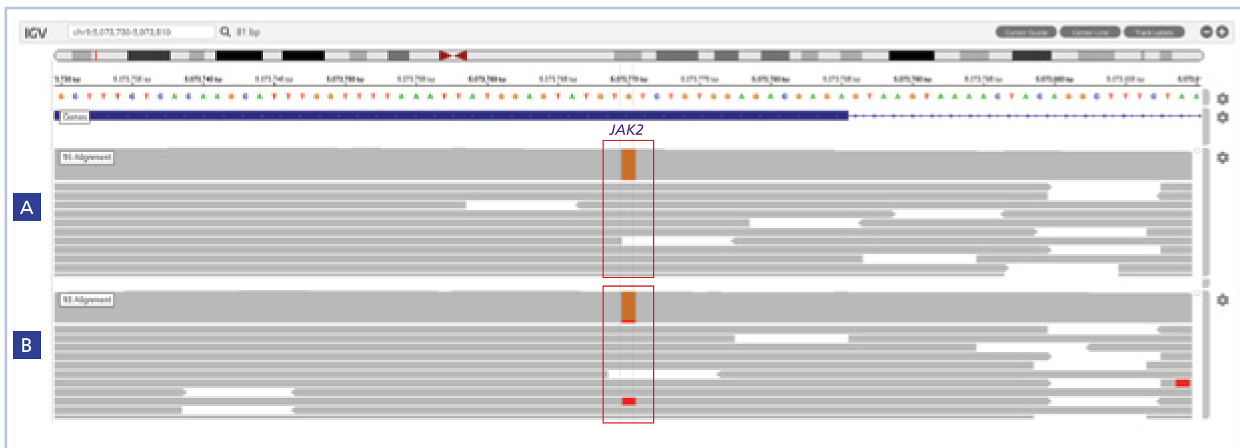


Figure 2: Detection of low frequency somatic variants, as **A** 1% and **B** 9% *JAK2* V617F mutations using a SureSeq Myeloid Panel.

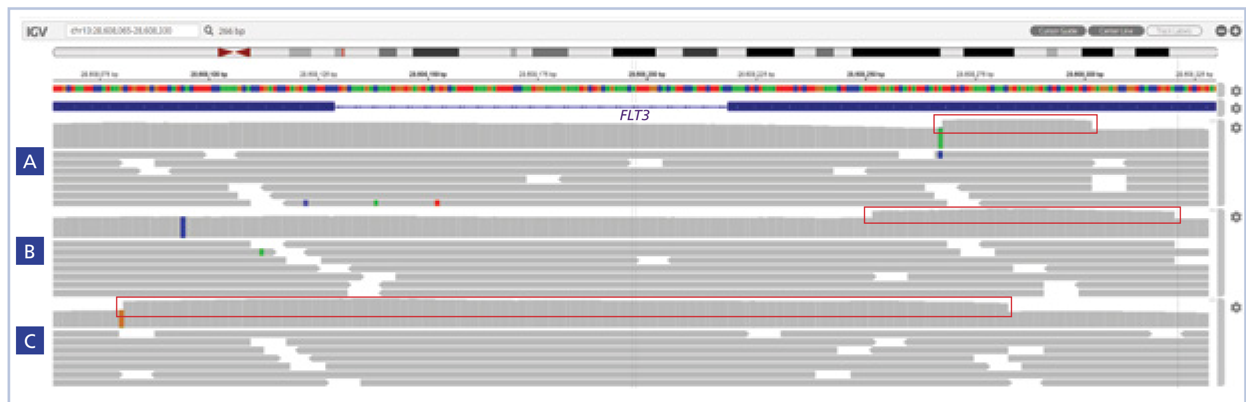
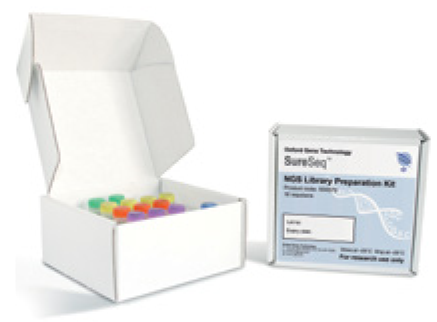


Figure 3: Detection of *FLT3* ITDs of difference sizes, **A** 33 bp, **B** 69 bp, **C** 201 bp, using a SureSeq myPanel Custom AML Panel. Note how OGT's innovative panel design in conjunction with Interpret is able to identify and call ITDs much longer than the sequencing read length of 150 bp.

SureSeq™

Cat. No. **500084** (16 reactions)
Cat. No. **500085** (48 reactions)

SureSeq NGS Library Preparation Kit



The complete library preparation solution for unparalleled next generation sequencing (NGS) results.

The SureSeq NGS Library Preparation Kit generates NGS libraries suitable for the capture of targeted genomic regions using hybridisation. With a streamlined workflow, significantly reduced hands-on steps and hybridisation times as low as 30 minutes, SureSeq offers all of the benefits of hybridisation in as little as a 1-day workflow. The SureSeq NGS Library Preparation Kit delivers high performance in the quality metrics that really matter, giving more reliable, more trustworthy data. Exceptionally low levels of duplication (Figure 2) ensures more accurate calling, more even coverage and higher levels of confidence in the data produced.

The inclusion of the SureSeq Hyb & Wash buffer, optimised for use with SureSeq NGS panels, simplifies this key step while offering excellent coverage uniformity (Figure 3) and reproducibility. It contains all the components ready-to-use to perform the hybridisation and wash steps in SureSeq sequence capture protocols, eliminating the requirement to dilute buffers and the possibility of cross-contamination during buffer preparation.

SureSeq myPanel offers:

- Greater trust in your data — high performance with low duplication rates, high sequence quality and high percentage of on-target bases
- Simpler hybridisation — all components of the SureSeq Hyb & Wash buffer are ready-to-use with no requirement for multiple wash buffers
- Rapid process — streamlined protocol, minimal manual handling, automation and a rapid hybridisation step offers increased reliability as well as throughput
- Reliable results — NGS targeted panel, complete NGS library preparation solution and powerful

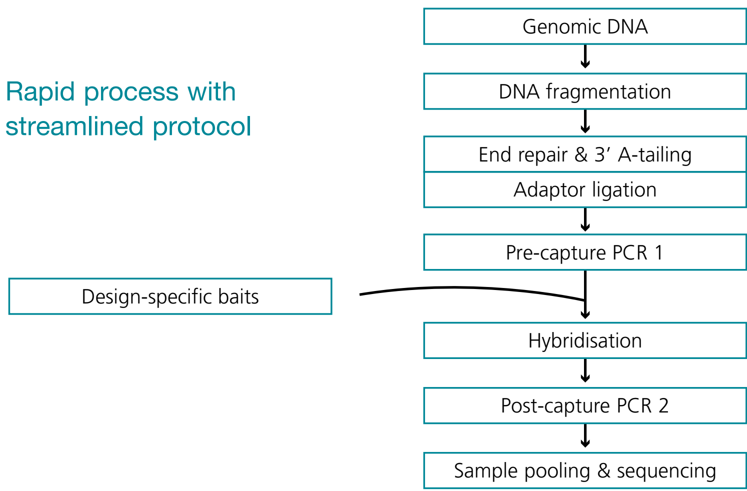


Figure 1: A streamlined protocol, including enrichment by hybridisation. The complete procedure can be completed in 1.5 days with minimal handling time.

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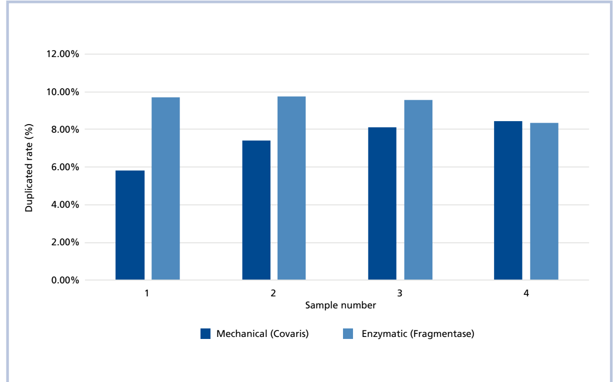

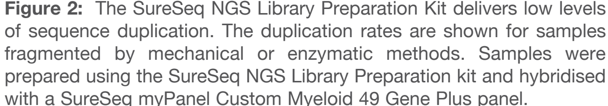

Figure 2: The SureSeq NGS Library Preparation Kit delivers low levels of sequence duplication. The duplication rates are shown for samples fragmented by mechanical or enzymatic methods. Samples were prepared using the SureSeq NGS Library Preparation kit and hybridised with a SureSeq myPanel Custom Myeloid 49 Gene Plus panel.

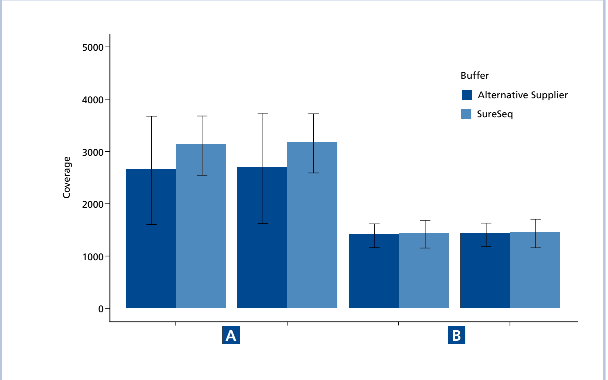

Figure 3: Superior performance. Comparison of the mean target coverage generated using the SureSeq Hyb & Wash Buffer Kit (light blue) compared to an alternative supplier kit (dark blue). **A** SureSeq myPanel custom CLL panel and **B** SureSeq myPanel custom CLL plus CNV panel.

Ordering information

Product	Contents	Cat. No.
SureSeq NGS Library Preparation Complete Solution (16)	Bundle of 1x SureSeq library preparation kit (16), containing adaptors, PCR primers and enzymes, 1x SureSeq Solution (16) NGS Index Kit – Collection A, 1x SureSeq Hyb & Wash Kit (16), 1x Dynabeads M270 Streptavidin (2ml) and 1x AMPure XP beads (10ml). Sufficient for 16 samples	500084
SureSeq NGS Library Preparation Complete Solution (48)	Bundle of 3x SureSeq NGS Library Preparation Kit (16), containing adaptors, PCR primers and enzymes, 1x SureSeq Solution (48) NGS Index Kit – Collection B, 3x SureSeq NGS Hyb & Wash Kit (16), 3x Dynabeads M270 Streptavidin (2ml) and 3x AMPure XP beads (10ml). Sufficient for 48 samples	500085
SureSeq NGS Library Preparation and Hyb & Wash Kit (16)	Bundle of 1x SureSeq NGS Library Preparation Kit (16), containing adaptors, PCR primers and enzymes, 1x SureSeq Hyb & Wash Kit (16) NGS Index Kit – Collection A and 1x SureSeq Hyb & Wash Kit (16). Sufficient for 16 samples	500082
SureSeq NGS Library Preparation and Hyb & Wash (48)	Bundle of 3x SureSeq NGS Library Preparation Kit (16), containing adaptors, PCR primers and enzymes, 1x SureSeq NNGS Index Kit - Collection B and 3x SureSeq Hyb & Wash kit (16). Sufficient for 48 samples	500083
SureSeq NGS Library Preparation Kit (16)	Bundle of 1 x library preparation kit (16), containing adaptors, PCR primers and enzymes sufficient for 16 samples and 1 x SureSeq NGS Index Kit – Collection A	500070
SureSeq NGS Library Preparation Kit (48)	Bundle of 3 x library preparation kit (16), containing adaptors, PCR primers and enzymes sufficient for 48 samples and 1 x SureSeq NGS Index Kit – Collection B	500073
SureSeq NGS Hyb & Wash Kit (16)	Hybridisation buffer, Wash buffer, Cot and blocking oligos. Sufficient for 16 samples	500075
SureSeq NGS Hyb & Wash Kit (48)	Bundle of 3x SureSeq NGS Hyb & Wash Kit (16), containing Hybridisation buffer, Wash buffer, Cot and blocking oligos. Sufficient for 48 samples	500086

The SureSeq NGS Library Preparation Kit was jointly developed between Oxford Gene Technology and Bioline Reagents Limited.

Cat. No. **500079** (16 reactions)*

SureSeq FFPE DNA Repair Mix

SureSeq FFPE DNA Repair Mix:

- Optimised to repair a broad range of damage in FFPE-derived DNA — remove artefacts caused by fixation and long-term storage
- Improves NGS library yields, %OTR and mean target coverage — get excellent sequencing data for confident variant calling from FFPE DNA
- Allows decreased amount of input DNA — preserve your precious samples and get meaningful results from as little as 100 ng of FFPE DNA

Tissue biopsies are typically archived as formalin-fixed, paraffin-embedded (FFPE) blocks, which preserve tissue morphology and allow long-term storage at room temperature. However, the methods used for fixation significantly damage and compromise the quality of nucleic acids from these samples. Consequently, it may be difficult to distinguish between true and damage-induced low-frequency mutations in such samples. The SureSeq FFPE DNA Repair Mix is a mixture of enzymes that has been optimised to remove a broad range of damage that can cause artefacts in sequencing data (Table 1).

Damage	Repaired?
Deamination of cytosine to uracil	✓
Nicks and gaps	✓
Oxidised bases	✓
Blocked 3' ends	✓
DNA fragmentation	✗
DNA-protein crosslinks	✗

Table 1: The SureSeq FFPE DNA Repair Mix is capable of removing a variety of DNA damage caused by fixation and long-term storage.

The SureSeq FFPE DNA Repair Mix has been shown to significantly improve NGS library yields, preserving original complexity and delivering high-quality sequencing data for confident calling of variants with low minor allele fractions (MAFs). It also increases depth of coverage and %OTR improving sensitivity of your test (Figure 1).

Pathology labs often have to work with very limited amounts of material. Additionally, FFPE samples are usually irreplaceable. This leads to the need to reduce DNA input in downstream applications including NGS. Often amplicon-based approaches are chosen as they require very little input material. Unfortunately, due to PCR bias and lower complexity from smaller input amounts, these methods are not well suited to detect low-frequency mutations in heterogeneous tumour samples. Hybridisation-based approaches eliminate the problem of PCR bias providing much more reliable data but they typically require higher DNA inputs of 500 ng – 1 µg. Using the SureSeq FFPE DNA Repair Mix a reduction in the amount of starting material down to 100 ng depending on required depth of coverage is possible.

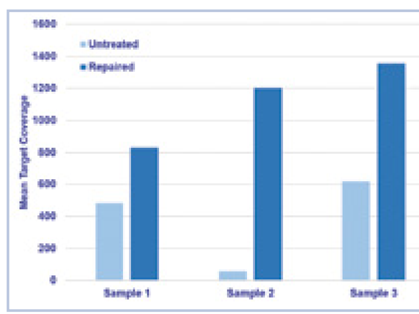

Figure 1: The SureSeq FFPE DNA Repair Mix significantly improves mean target coverage resulting in more confident calls. Data obtained using 500ng of FFPE DNA from ovarian and colon cancer samples; 16 samples per MiSeq lane.

*The SureSeq™ FFPE DNA Repair Mix can only be purchased in conjunction with SureSeq NGS panels, not as a standalone product.

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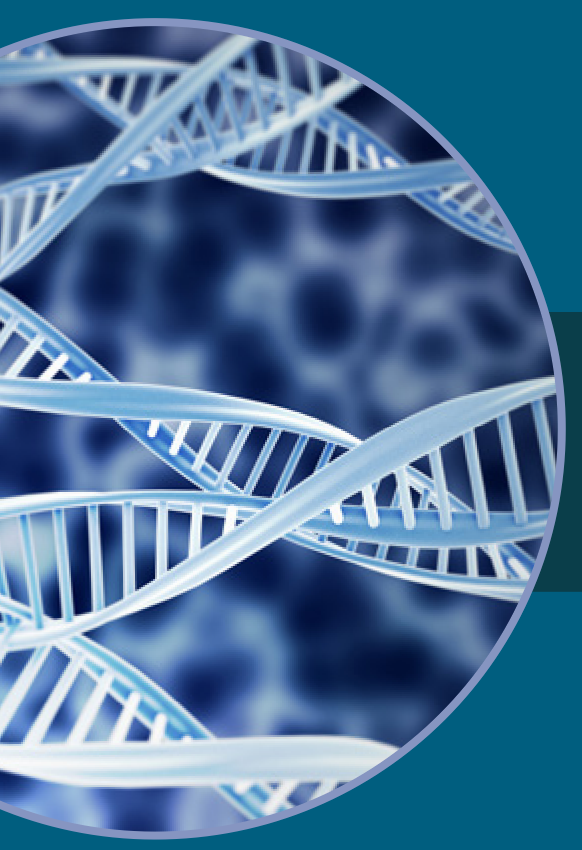
CytoSure NGS and Array Products

CytoSure™



NGS & Array Products for Cytogenetics and Rare Disease

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Constitutional Arrays

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CytoSure Disease-Focused Arrays

195 CytoSure Medical Research Exome Array
197 CytoSure Autism Research Array
198 CytoSure Cardiomyopathy Research Array
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199 CytoSure Eye Disease Research Array
200 CytoSure NMD Research Array

201 CytoSure Cancer +SNP Arrays

204 CytoSure Custom Designed aCGH Arrays
205 CytoSure Interpret Software
207 CytoSure Genomic DNA Labelling kits
209 CytoSure Sample Tracking Spike-ins
210 Accessories

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Overview

The CytoSure™ brand offers comprehensive microarray and Next Generation Sequencing (NGS) solutions for research into a wide range of genetic aberrations, including constitutional and molecular disorders.

For a number of years, array comparative genomic hybridisation (aCGH) has been considered the primary technique for research into copy number variation (CNV) and loss of heterozygosity (LOH) analysis in cytogenetic and rare disease samples. CytoSure microarrays have been designed and optimised to provide the best analysis possible, offering genome-wide coverage and single-exon resolution, facilitating accurate detection of microdeletions and duplications. Probe design and development is critical and OGT's probe design algorithms have allowed us to generate an Oligome™ database of ~26.5 million optimised probes to select from, ensuring optimal probe selection and array performance. All our array products include our class-leading CytoSure Interpret software for fast and simple interpretation of your data.

Building on our experience with CNV and LOH calling from our array offering, OGT has developed the CytoSure NGS platform, which includes the CytoSure Constitutional NGS panel and the Familial Hypercholesterolemia (FH) panels, adding the benefit of SNV and indel analysis capability. The CNV calling performance has been made possible by excellent panel design, in tandem with state-of-the-art analytical software. The CytoSure Constitutional NGS panel has been designed to offer a comprehensive targeted intellectual disability (ID) and developmental delay (DD) genetic assay — with over 700 ID/DD genes targeted at the exon level and a backbone of additional targets spread throughout the genome. It enables the seamless transition from microarrays to NGS, delivering a significant increase in information obtained from a single assay without extensive analysis time and costly data generation and storage.

For more information, visit **www.ogt.com/CytoSure**

CytoSure™

Cat. No. **502005-B24** (24 reactions)
Cat. No. **502005-B96** (96 reactions)

CytoSure™ Constitutional NGS

Unparalleled CNV calling in a targeted Constitutional NGS panel.

The CytoSure Constitutional NGS solution delivers:

- The ability to detect CNV, SNV, indel, LOH, and mosaicism
- Advanced panel design and software
- Robust single-exon CNV calling unlike other large targeted panels or exomes
- The most up-to-date content for ID and DD
- A targeted >700-gene panel, minimising variants of uncertain significance (VUS) detection
- Regions across the genome are targeted to create a backbone of coverage
- Cost-effective analysis

Comprehensive aberration detection

The NGS panel is designed to cover important genes for ID/DD and also contains a backbone of baits covering common single nucleotide polymorphisms (SNPs), this allows detection of a comprehensive range of aberration types including CNVs, SNVs, indels and LOH in a single assay (Figure 1). This also includes detection within mosaic samples (Figure 2). The Interpret software (see page 181) user interface is conveniently arranged and also has the ability to switch between CNV/LOH calls and SNV/indel analysis, enabling a step-by-step approach to the interpretation process.

Advanced panel design and software for robust single-exon CNV calling

A key requirement in enabling the transition from a microarray-based technology to NGS for CNV detection is the ability to ensure that CNV data from the NGS panel is concordant with that from microarrays, particularly for small, sub-gene duplications and deletions. OGT's expertise in bait design ensures uniform sequencing coverage of the desired regions. This, coupled with Interpret's proprietary CNV calling algorithm, allows robust detection of even the smallest CNVs.

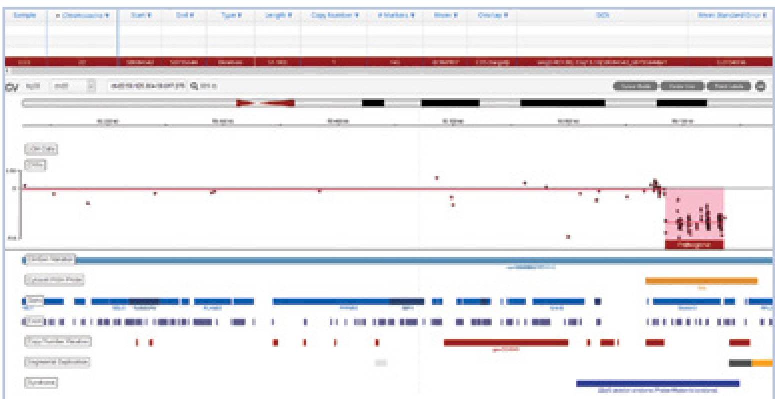

Figure 1: Detection of a 51kb deletion within the *SHANK3* gene on chromosome 22.*

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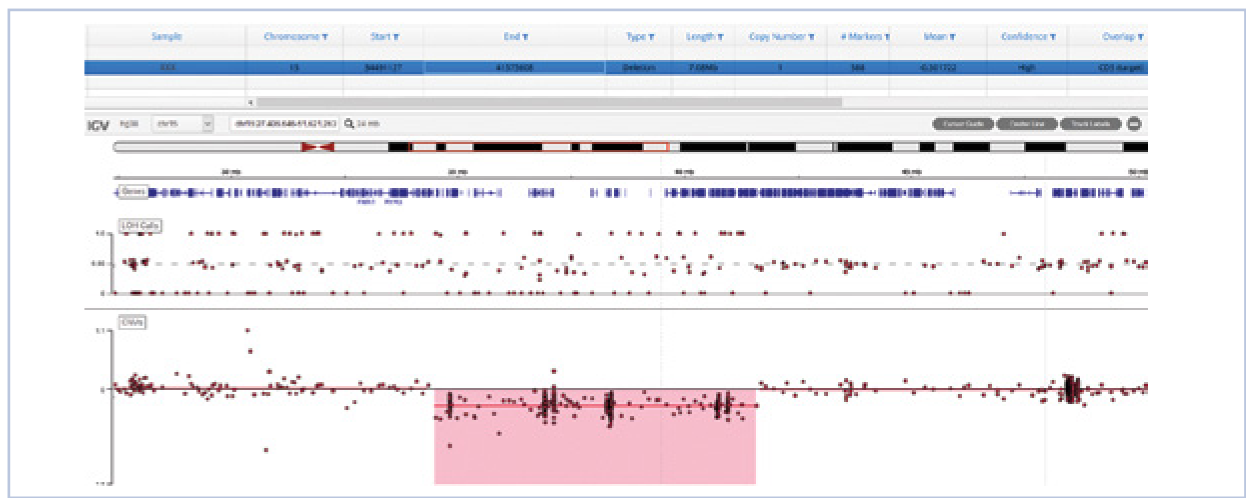

Figure 2: Sample with a 7Mb deletion at 15q14q15.1 within a mosaic sample.*

Ordering details and related products

For information on complimentary Interpret software, please see page 181.

Product	Contents	Cat. No.
CytoSure Constitutional NGS Solution (24)	Bundle of 1x CytoSure Constitutional NGS Panel (24), 1x CytoSure NGS Library Preparation Kit (24) and 1x CytoSure NGS Hybridisation & Wash Kit (24)	502005-B24
CytoSure Constitutional NGS Panel (24)	Enrichment baits sufficient for 24 samples	502003-24
CytoSure NGS Library Preparation Kit (24)	Library Preparation Kit containing adaptors, PCR primers and enzymes sufficient for 24 samples	502001-24
CytoSure NGS Hybridisation & Wash Kit (24)	Hybridisation buffer, Wash buffer, Cot and blocking oligos. Sufficient for 24 samples	502002-24
CytoSure Constitutional NGS Solution (96)	Bundle of 1x CytoSure Constitutional NGS Panel (96), 1x CytoSure NGS Library Preparation Kit (96) and 1x CytoSure NGS Hybridisation & Wash Kit (96)	502005-B96
CytoSure Constitutional NGS Panel (96)	Enrichment baits sufficient for 96 samples	502003-96
CytoSure NGS Library Preparation Kit (96)	Library Preparation Kit containing adaptors, PCR primers and enzymes sufficient for 96 samples	502001-96
CytoSure NGS Hybridisation & Wash Kit (96)	Hybridisation buffer, Wash buffer, Cot and blocking oligos. Sufficient for 96 samples	502002-96
CytoSure NGS Index Kit	48 Indexes sufficient for 4 reactions each	502004

* Clinical research sample provided courtesy of Centre hospitalier universitaire de Sherbrooke (CIUSSSE-CHUS)

CytoSure™ Comprehensive FH Panel

The CytoSure Comprehensive FH Panel facilitates the detection of exonic CNVs involved in Familial Hypercholesterolemia (FH) when used in conjunction with OGT's Interpret bioinformatics solution.

To date, most NGS CNV analysis approaches have been designed for whole genome/exome sequencing and besides being less robust than standard aCGH, they are not suitable for small targeted NGS panels. This is illustrated with the *LDLR* gene, thought to have a prevalence between 1/500 and 1/200[1] in FH. When intragenic CNVs detected using the panel were confirmed with aCGH (custom CytoSure arrays are available for confirmation of CNV detection), the concordance was 100% over the targeted exons of the NGS panel, offering confident and reliable CNV and SNV determination.

The CytoSure Comprehensive FH Panel offers:

- Confident variant detection, minimising the requirement for supplementary fill-in with Sanger sequencing
- Detection of CNVs as well as SNVs in a single assay — no need to run MLPA alongside your NGS panel
- Pre-optimised panels that meet your technical requirements — no more laborious in-house optimisation, decreasing assay development time

The hybridisation methodology, combined with our bait design expertise, allows generation of panels with outstanding completeness and coverage uniformity. Together, this allows the areas of CNV to be easily identified within each sample using our proprietary algorithm — delivering an increased understanding of the sample without an increase in cost or time.

All exons

LDLR	*LDLRAP1*	*APOB*	*PCSK9*
APOE	*LIPA*	*ABCG5*	*ABCG8*

REFERENCES

1. Brice, P; Burton, H; Edwards, CW; Humphries, SE; Aitman, TJ; (2013) Familial hypercholesterolaemia: A pressing issue for European health care. Atherosclerosis, 231(2), pp. 223-226.

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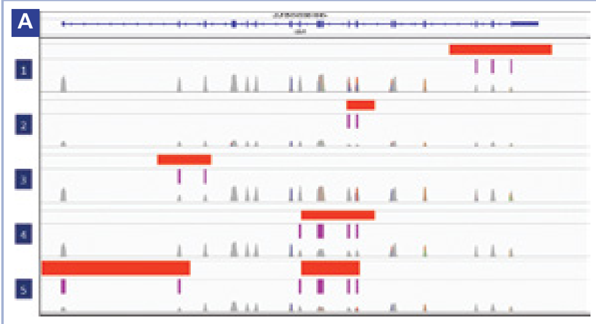
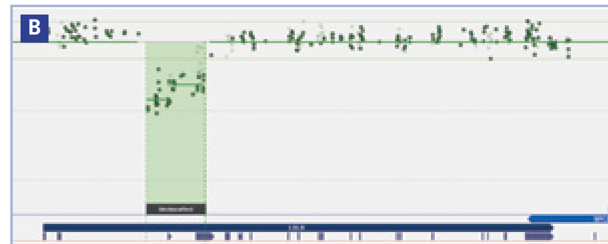


Figure 1: CNV in *LDLR* gene shown using IGV from the Broad Institute **A**: Red bars indicate areas of CNV (data from aCGH), purple bars represent deleted exons (data from NGS): 5 samples are shown, each with at least one area of CNV. There is complete concordance between the aCGH and NGS data. Note the evenness of the NGS coverage (even peak height) across each exon, allowing the areas of CNV to be easily identified. The data from the custom CytoSure aCGH array, confirms the deletions in *LDLR*. **B** A 2 exon deletion and **C**, a deletion of 2 exons and 4 exons, corresponding to samples 3 and 5 in **A** respectively.



Ordering details and related products

For information on complimentary Interpret software, please see page 181.

Product	Contents	Cat. No.
CytoSure Comprehensive FH Panel (16 reactions)	Enrichment baits; Interpret Software	601004-16
CytoSure Comprehensive FH Panel (96)	Enrichment baits; Interpret Software	601004-96
SureSeq NGS Library Preparation Kit (16)	Bundle of 1x library preparation kit (16) containing adaptors, PCR primers and enzymes sufficient for 16 samples and 1x SureSeq NGS Index Kit – Collection A	500070
SureSeq NGS Library Preparation Kit (48)	Bundle of 3x library preparation kit (16), containing adaptors, PCR primers and enzymes sufficient for 48 samples and 1x SureSeq NGS Index Kit – Collection B	500073

CytoSure Constitutional v3 and v3 + LOH arrays

Enhanced exon-level coverage of developmental disorder genes and the latest ClinGen* and DDD content.

The CytoSure Constitutional v3 arrays deliver:

- Up-to-date developmental disorder content — all the latest research-validated genes and regions
- Single exonic CNV detection in the genes that matter — enabling high resolution CNV detection in up to 502 genes of interest
- Integrated sample tracking probes and optimised labeling kits — the complete solution for reliable analysis and reporting
- Streamlined data analysis and interpretation — straightforward and fast analysis of CNVs and LOH

Enhanced exon-level coverage of all developmental disorders and the latest ClinGen and DDD content

CytoSure Constitutional v3 arrays have been developed in collaboration with experts at the Wellcome Trust Sanger Institute. These unique arrays combine the most up-to-date and relevant developmental delay content from the recent Deciphering Developmental Disorders (DDD) study with the latest updates from ClinGen the Clinical Genome Resource[1].

Higher probe density across the exons and introns of important developmental delay genes allows improved detection of small (<500bp) deletions and duplications that might otherwise be missed or require manual calling on other constitutional cytogenetics array designs (Figures 1 and 2). An informed, sophisticated approach to array design has been used, with more probes being located in regions of the genome that are most likely to detect a biologically relevant aberration (Table 1).The addition of a research-validated collection of single nucleotide polymorphism (SNP) probes on the CytoSure Constitutional v3 +LOH array facilitates the precise identification of loss of heterozygosity (LOH) and uniparental disomy (UPD) in addition to accurate copy number (CN) detection.

Streamlined data analysis and interpretation

CytoSure Interpret Software, provided free of charge with all CytoSure arrays, is a powerful, easy-to-use package for the analysis of CNV and SNP data which includes a host of innovative features to enable the automation of data analysis workflows.

CytoSure Constitutional v3 arrays are available in a range of formats to match your resolution and throughput requirements. All CytoSure arrays have been research-validated using CytoSure Genomic DNA Labelling Kits.

REFERENCES

1. NCBI (2015) ClinGen Dosage Sensitivity Map [online] Available from: http://ncbi.nlm.nih.gov/projects/dbvar/clingen [Accessed 28 May 2015]

* Formerly known as ISCA/ICCG.

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CytoSure™

	Format	Cat. no.	Top priority genes	Medium priority genes	Lower priority genes	Decipher Syndrome regions	ClinGen regions	High priority backbone resolution	Medium priority backbone resolution	Low priority backbone resolution	LOH resolution
CytoSure Constitutional v3	8x60k	020045	Exon targeted	Whole-gene targeted	Whole-gene targeted	Whole-gene targeted	Whole-gene targeted	189kb	375kb	663kb	-
CytoSure Constitutional v3	4x180k	020046	Exon targeted	Exon targeted	Exon targeted	Whole-gene targeted	Whole-gene targeted	68kb	74kb	162kb	-
CytoSure Constitutional v3 +LOH	4x180k	020047	Exon targeted	Whole-gene targeted	Whole-gene targeted	Whole-gene targeted	Whole-gene targeted	68kb	74kb	162kb	7Mb and above

Table 1: Selection guide for CytoSure Constitutional v3 arrays. For a complete list of genes covered, please email: products@ogt.com

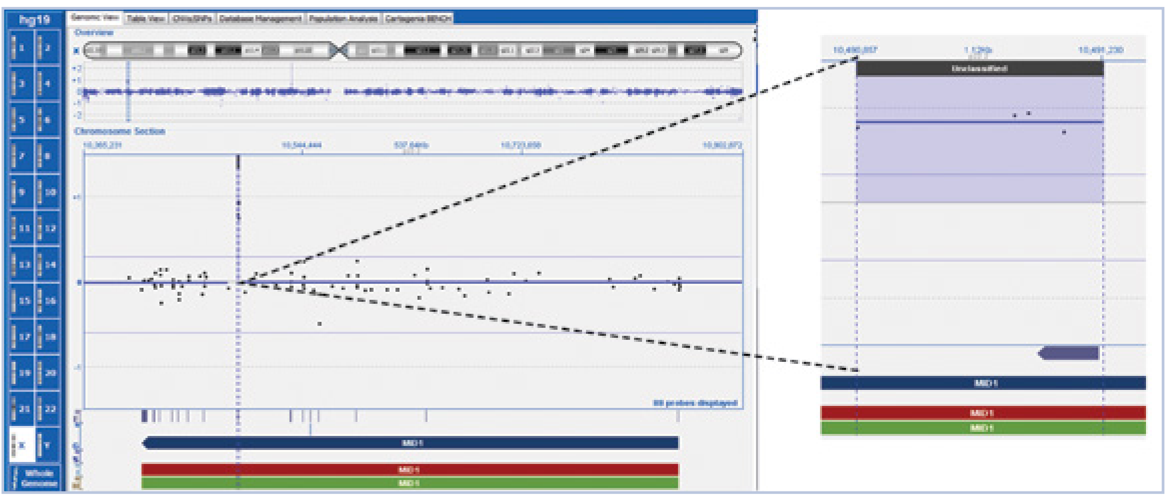

Figure 1: Accurate detection of a small, single-exon (<500bp; 4 probes) duplication in *MID1* associated with Opitz-G syndrome.*

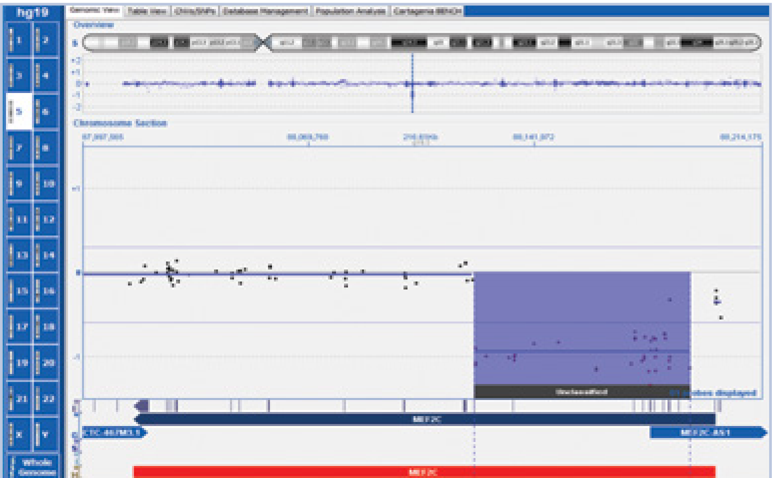

Figure 2: Enhanced probe coverage. A 68kb deletion covering *MEF2C* gene. The CytoSure Constitutional v3 8x60k array contains 36 probes in this region. This deletion was previously called manually on the CytoSure ISCA v2 8x60k array which has only 2 probes in this deletion.*

* Data kindly provided by West Midlands Regional Genetics Laboratory (WMRGL) Birmingham UK.
Find out more at www.ogt.com/cytosure

Cat. No. **020100** (1x1M)

CytoSure Medical Research Exome Array

Complete coverage of all medically relevant genes; ultra-high resolution, exon-focused CNV calling in inherited molecular disease.

CytoSure Medical Research Exome array delivers:

- Highly targeted optimised probes — detect single or multiple exonic CNVs
- Medical research relevant content — over 4600 hand-curated, research-validated genes
- Optimised labelling kits and integrated sample tracking probes — for confident analysis and reporting
- Combine with NGS exome analysis — comprehensive mutation spectrum analysis in rare disease

The CytoSure Medical Research Exome Array is a highly targeted exon-focused array capable of detecting medically relevant microdeletions and microduplications. Developed in collaboration with leading molecular genetics experts at Emory University, this array covers the most medically relevant regions of the genome gathered from their research into molecular disorders. The Medical Research Exome Array makes an ideal complement to an exome sequencing approach to provide a comprehensive mutation spectrum analysis in rare disease.

Highly targeted optimised probes

All probes were tested *in silico* and scored on quality before the highest scoring probes were printed on an array and tested in the laboratory. Only the most accurate, best performing probes were used in the final design. Probes have been selected to target the exonic regions of 4,645 genes. For the majority of genes there are a minimum of 4 probes per exon. For very large exons, probes are distributed evenly along the exon with one probe every 125bp. For any array design, good backbone coverage is important to ensure accurate normalisation. In the untargeted backbone, the CytoSure Medical Research Exome array has one probe every 42kb. Industry-leading coverage levels have been achieved with this design process — 88% of genes have 100% coverage, with 98% of genes having >75% coverage.

All probes in the Medical Research Exome Array can be used to create customised, high value, disease-specific arrays in multiplex formats (see page 204). Emory University has used this approach to create disease-specific arrays, each of which is also available as a catalogue product (see pages 198-200).

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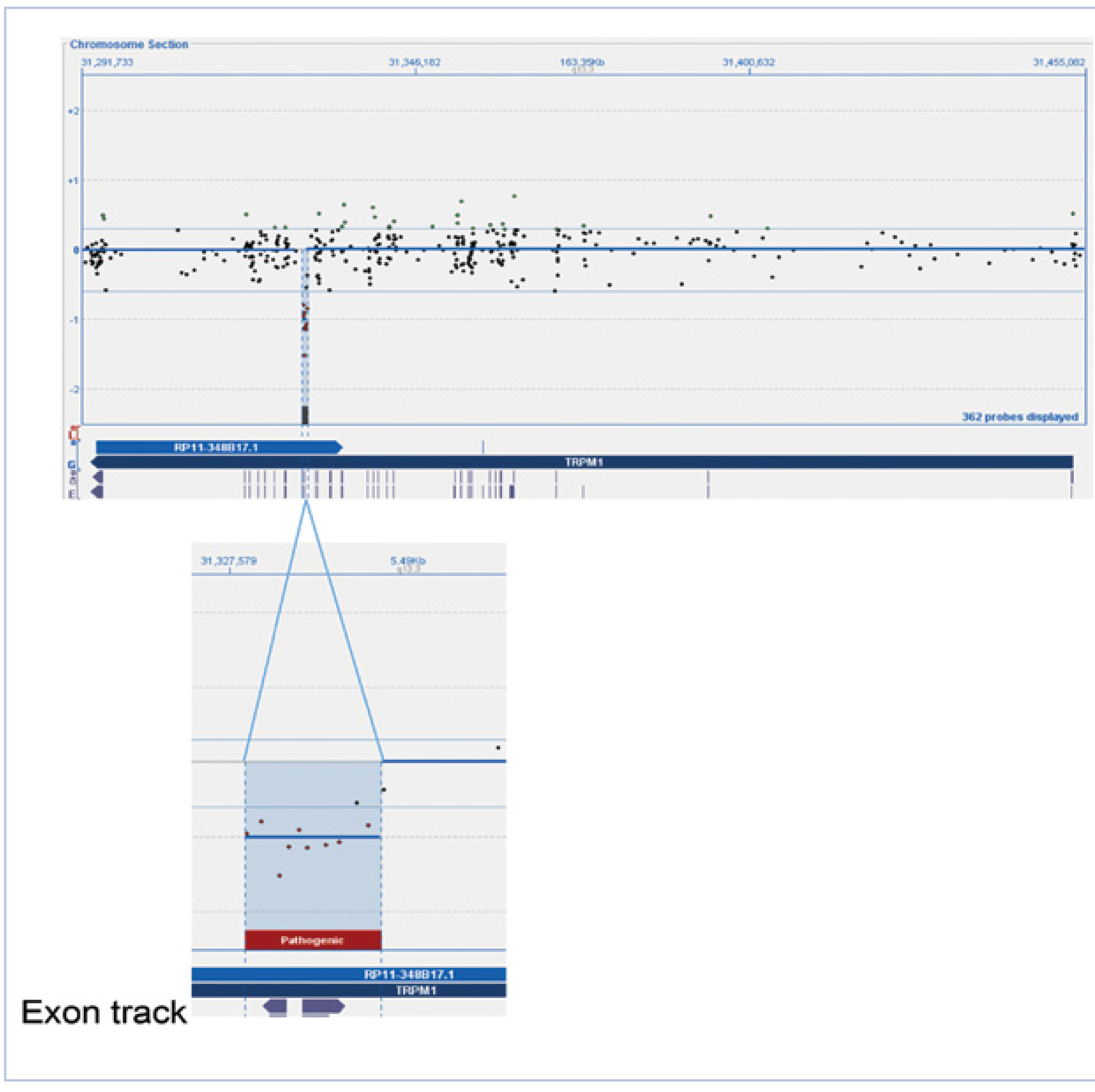

Figure 1: CytoSure™ Interpret Software clearly displays small aberrations and enables easy identification of genes and exons. Mutations in *TRPM1* may be associated with congenital stationary night blindness. Shown here in the top panel is an overview of the whole gene. In the bottom panel, the close-up view shows a very small 684bp deletion which contains 10 probes, and also spans a single exon*.

* Data kindly provided by Madhuri Hegde, Ph.D., FACMG, Emory University.

CytoSure Disease-focused Arrays

Ultra-high resolution, exon-focused CNV calling for specific inherited molecular disease.

CytoSure Disease-Focused arrays deliver:

- Accurate detection of copy number variation at the exon-level — a perfect complement to sequencing analysis
- Array content taken from the Medical Research Exome Array — fully optimised and research-validated by Emory University
- Multiplex (4x180k) format is cost-effective and allows for higher sample throughput
- Easy data interpretation using optimised protocols for high signal-to-noise ratios and industry-leading CytoSure Interpret Software

Array content fully optimised and research-validated

CytoSure disease-focused research arrays are designed to accurately identify small intragenic copy number variations (CNVs). They are exon-focused, high-resolution, 4x180k aCGH (array comparative genomic hybidisation) array designs covering medically-relevant genes for research into specific disorders. The content for the disease-focused research arrays has been designed and optimised in collaboration with leading molecular genetics experts at Emory University.

For the best results, combine the CytoSure disease-focused arrays with the CytoSure Genomic DNA labelling kits (page 207) and CytoSure Interpret Software (page 205).

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CytoSure™ Cat. No. **700121** (4x180k)

CytoSure Autism Research Array

Autism spectrum disorders (ASD) affect 21.7 million people globally[1]. CNV linked to ASD have been described at 11 loci across 8 chromosomes[2], hence understanding CNV status is critical for research into the genetic basis of this disease.

- 227 genes covered
- Diseases covered by the array:
  - Autism
  - Hearing loss
  - XLID (X-linked intellectual disability)

REFERENCES

1. Global Burden of Disease Study 2013 Collaborators (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386 (9995), 743-800
2. Menasha, I. *et al* (2013) Prioritization of Copy Number Variation Loci Associated with Autism from AutDB–An Integrative Multi-Study Genetic Database. PLOS one 8 (6), e66707

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CytoSure™ Cat. No. **700110** (4x180k)

CytoSure Cardiomyopathy Research Array

CNVs are associated with a number of cardiomyopathies, including Long QT syndrome (LQTS)[1,2] and dilated cardiomyopathy (DCM)[3], so it is important to include CNV into any research. The array includes genes that cause genetic syndromes with cardiomyopathy as a feature (e.g. Duchenne/ Becker MD, Emery-Dreifuss MD).

- 223 genes covered
- Examples of diseases covered by the array:
  - Cardiomyopathies including LQTS (Long QT syndrome), DCM (dilated cardiomyopathy), LVNC (left ventricular non-compaction)
  - Hereditary neuropathies
  - Connective tissue disorders

REFERENCES

1. Eddy, C.A. *et al*. (2008) Identification of large gene deletions and duplications in KCNQ1 and KCNH2 in patients with long QT syndrome. Heart Rhythm 5, 1275 -1281
2. Tester, D.J. *et al*. (2010) Prevalence and spectrum of large deletions or duplications in the major long QT syndrome-susceptibility genes and implications for long QT syndrome genetic testing. Am J Cardiol 106, 1124 -1128
3. Norton, N. *et al*. (2011) Genome-wide studies of copy number variation and exome sequencing identify rare variants in bag 3 as a cause of dilated cardiomyopathy. Am J Hum Genet. 88, 273-82

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Cat. No. **700112** (4x180k)

CytoSure Epilepsy Research Array

While over 200 single-gene defects have been described in epilepsy[1], CNVs also play a key role in this disease. An important study identified 437 CNVs in 323/805 (40%) individuals with epilepsy (1–4 per patient) ranging from 18kb to 142Mb in size[2], many of which were associated with the disease.

- 212 genes covered
- Examples of diseases covered by the array:
  - Epilepsy
  - Brain malformations
  - SCID (severe combined immune deficiency)

REFERENCES

1. Kumar, D. ed. (2008) Genomics and clinical medicine. Oxford: Oxford University Press. p. 279.
2. Olson, H. *et al* (2014) Copy number variation plays an important role in clinical epilepsy. Annals of Neurology 75(6), 943–958

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Cat. No. **700113** (4x180k)

CytoSure Eye Disease Research Array

The CytoSure Eye Disease Research Array includes genes important for syndromic and non-syndromic inherited retinal and choroidal dystrophies, as well as ocular developmental disorders.

- 221 genes covered
- Examples of diseases covered by the array:
  - Retinitis pigmentosa
  - Stargardt disease
  - Congenital stationary night blindness
  - Usher syndrome

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CytoSure™ Cat. No. **700117** (4x180k)

CytoSure NMD Research Array

It is estimated that around 16/10,000 of the population are affected by some form of neuromuscular disease (NMD)[1]. The CytoSure NMD Research array is focused primarily on the muscular dystrophies. In the most common form of muscular dystrophy, Duchenne muscular dystrophy, between 60% and 75% of disease relevant mutations are CNVs[2].

- 205 genes covered
- Examples of diseases covered by the array:
  - DMD (Duchenne muscular dystrophy)
  - Limb girdle MD
  - CMD (Congenital muscular dystrophy)
  - Emery-Dreifuss MD
  - Congenital disorders of glycosylation
  - MODY (Maturity onset diabetes of the young)

REFERENCES

1. Deenen, J.C.W. *et al* (2015) The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. Journal of Neuromuscular Disease 2(1) 73-85
2. Prior, T.W. and Bridgeman, S.J. (2005) Experience and Strategy for the Molecular Testing of Duchenne Muscular Dystrophy. J Mol Diagn. 7(3) 317-26

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CytoSure™

Other disease-focused research arrays

Other disease focused arrays are also available including arrays focused on:

- Ciliopathies 4x180k
- Metabolic disorders 4x180k
- Skeletal dysplasia 4x180k
- Hereditary cancer 4x180k
- Duchenne muscular dystrophy (DMD) 8x60k

See **www.ogt.com/CytoSure** for more information.

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Haematological Cancer +SNP: Cat. No. **020070** (8x60k)

Cancer +SNP: Cat. No. **700090** (4x180k)

Consortium Cancer +SNP: Cat. No. **020071** (4x180k)

CytoSure Cancer +SNP Arrays

Reliable detection of copy number changes and loss of heterozygosity (LOH) on a single array for haematological malignancies and solid tumours.

CytoSure Cancer +SNP arrays deliver:

- Unique SNP probe technology allowing the use of any reference sample with no restriction digest
- Unparalleled performance through design optimisation
- Fast and easy analysis using CytoSure Interpret software
- Versatile array designs across a choice of formats

Unique SNP Probe technology allows the use of any reference sample with no restriction digest

CytoSure Cancer +SNP arrays combine aCGH (array comparative genomic hybridisation)-based CNV detection with fully research-validated SNP content allowing confident and cost-effective CNV and LOH identification using a single array (Figure 1). Due to the unique design of the SNP probes where an intensity-based comparison is made between the two SNP alleles there are no changes to the standard aCGH protocol, no restriction digest is required and any reference sample can be used. The ability to use matched reference samples (e.g. buccal swab tissue from the same individual) is particularly important when investigating aberrations in cancer as it enables constitutional abnormalities to be filtered out.

Improved results over other technologies

Array comparative genomic hybridisation (aCGH) using 60-mer oligonucleotide probes has been shown to offer higher signal-to-noise ratios, increased sensitivity and increased specificity compared to other technologies[1].

With other platforms, the use of 60-mer technology for LOH analysis typically requires a restriction digest, which can compromise sample quality, limits the target SNPs to those overlapping restriction sites, and requires a genotyped reference for comparison. However, due to OGT's unique SNP technology, there is no restriction digest required, the most informative SNPs can be targeted and any reference sample can be used (e.g. normal tissue from the same individual to enable constitutional abnormalities to be filtered out).

Combined with the *in silico* and empirical optimisation carried out across all OGT catalogue arrays as well as easy customisation to include any additional regions of interest, OGT's Cancer +SNP arrays deliver flexible and robust analysis of CNV and LOH combined in a single assay.

REFERENCES

1. Curtis, C. *et al* (2009) The pitfalls of platform comparison: DNA copy number array technologies assessed. BMC Genomics 10, 588-610
2. Hurles, M. *et al* (2010) Characterising and predicting haploinsufficiency in the human genome. PLoS Genetics 6, 10, e1001154 1-11.

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Fast and easy analysis using CytoSure Interpret Software

OGT's CytoSure Interpret Software, which accompanies all CytoSure arrays, is a powerful and easy-to-use package for straightforward analysis of CNV and SNP data (Figure 1), delivering:

- Feature-rich, highly-customisable analysis workflows to meet any lab's requirements
- Automation of the data analysis processes, including batch upload of LIMS information to the database
- Extensive cancer-specific annotation tracks including regions from the Mitelman Database, the Cancer Gene Consensus Genes, the Atlas of Genetics and Cytogenetics in Oncology and Haematology and the Hurles Haploinsufficiency data[2].

For more information on complimentary CytoSure Interpret Software, see page 205.

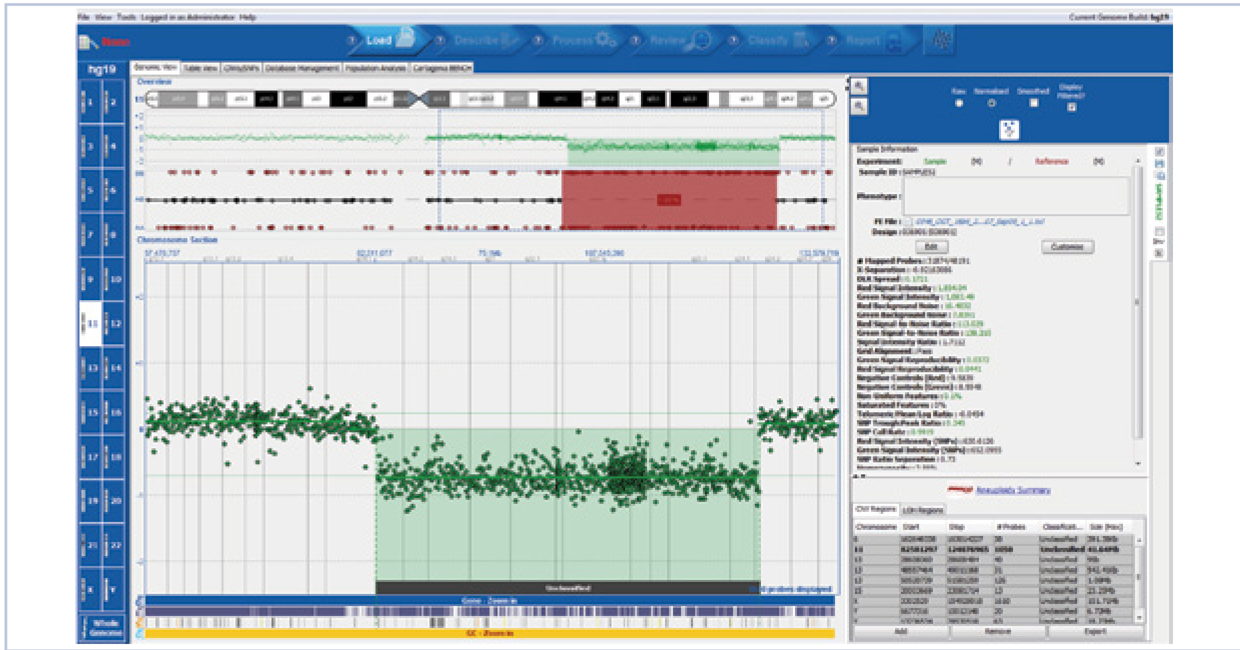

Figure 1: Shown here is a CLL research sample run on the CytoSure Consortium Cancer +SNP array (8x60k) with a deletion and corresponding LOH. CytoSure Interpret offers an intuitive user interface for easy interpretation of genetic findings. Samples kindly provided by Dr Jon Strefford, University of Southampton.

Versatile array designs across a choice of formats

Three fully customisable Cancer +SNP designs are available, designed using different formats to suit any analysis and throughput requirement.

Array	Copy number resolution		LOH resolution
	Backbone	Average gene resolution (Hg19)	
CytoSure Haematological Cancer +SNP (8x60k)	1 probe every 117kb	1 probe every 68kb	30Mb
CytoSure Cancer +SNP (4x180k)	1 probe every 44kb	1 probe every 25kb	20Mb
CytoSure Consortium Cancer +SNP (4x180k)	1 probe every 36kb	1 probe every 23kb	10Mb

Table 1: CytoSure Cancer +SNP arrays selection guide. For a complete list of genes covered by each array, email support@ogt.com

* Samples kindly provided by Dr Jon Strefford, University of Southampton.

CytoSure Haematological Cancer +SNP array (8x60k)

This design offers a balance between throughput and resolution, allowing investigation of large CNV and LOH in a cost-effective manner.

This array delivers:

- Whole-genome coverage for CNV and LOH analysis
- Enhanced resolution across regions relevant for research into CLL, MM, MPN and MDS (Chronic Lymphocytic leukaemia, Multiple Myeloma, Myeloproliferative Neoplasms, Myelodyspastic Syndromes)

CytoSure Cancer +SNP array (4x180k)

This design, developed in collaboration with Prof. Jacqueline Schoumans (Head of the Cancer Cytogenetic Unit at Lausanne University Hospital), focusses on CNV detection across the target regions.

This array delivers:

- Whole-genome coverage for CNV and LOH analysis
- Whole-gene CNV resolution across more than 1500 cancer-associated genes
- Exon resolution across 18 genes

CDKN2A	*IKZF1*	*NRAS*
CDKN2B	*IK2F2*	*PAX5*
CEBPA	*JAK2*	*RB1*
EBF1	*KIT*	*RUNX1*
ETV6	*MPL*	*TET2*
FLT3	*NF1*	*WT1*

Table 2: Genes covered at single-exon resolution on the CytoSure Cancer +SNP array

CytoSure Consortium Cancer +SNP array (4x180k)

This design focuses on the content recommended by the Cancer Cytogenetics Microarray Consortium (CCMC) now known as the Cancer Genomics Consortium (CGC), with more probes dedicated to SNP analysis than the other arrays. The recommended content is intended to help standardise research across cancer genomics, similar to the successful model introduced by ISCA/ICCG, now known as ClinGen.

This array delivers:

- Whole-genome coverage for CNV and LOH analysis
- Enhanced coverage of 130 cancer-associated genomic regions
- Whole-gene CNV resolution of more than 500 cancer-associated genes

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CytoSure Custom Designed aCGH Arrays

Focused custom aCGH arrays designed to your specification by the microarray experts.

Custom arrays deliver:

- Complete confidence in the design of your array
- Flexible array content and format
- Customisation of any existing catalogue array
- Full custom designs including probes from our existing designs (e.g. Medical Research Exome Array), from our proprietary Oligome™ database, or new designs using our superior in-house design pipeline

High-quality aCGH arrays, perfectly matched to your exact specifications

CytoSure Custom arrays allow you to benefit from OGT's extensive array design expertise to produce an array matching your precise specifications. These arrays are ideal if you want to know the precise coordinates of an aberration by analysing specific areas of the genome at high resolution.

Complete confidence in the design of your array

OGT have designed hundreds of custom arrays for some of the world's leading researchers. The array content is selected from OGT's proprietary Oligome database — a database of more than 26.5 million oligonucleotide probes, or can be *de novo* designed using the proprietry OGT probe design pipeline. All *de novo* probes are in-silico optimised and optional empirical validation of the array content ensures optimal performance. A dedicated project manager from our experienced team of bioinformaticians is assigned to each new custom-design project. This gives a single point of contact throughout the process and ensures a close collaboration with our experts from initial consultation to delivery of the final design.

Flexible array content and format

CytoSure Custom arrays can be designed against any fully or partially sequenced genome as well as against sequencing data. In addition, OGT has extensively research-validated SNP content for detection of loss of heterozygosity (LOH) and uniparental disomy, which can be incorporated into the array design. CytoSure Custom arrays can be designed in a variety of formats depending on your desired level of focus, with 1, 2, 4, or 8 arrays available per slide to provide the most cost-effective solution for your research (Figure 1).

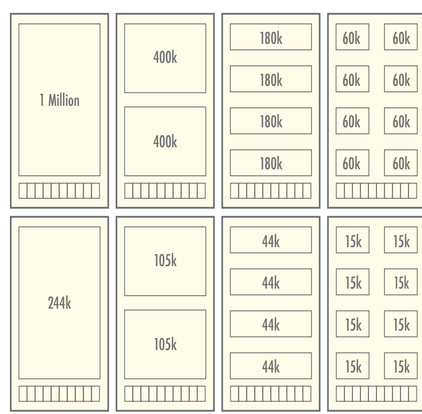

Figure 1: Multiple arrays on a single slide can reduce costs and improve efficiency.

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Included with all CytoSure microarrays

CytoSure™ Interpret Software

A powerful and easy-to-use package for analysis of aCGH (array comparative genomic hybridisation) data with multiple features allowing standardised data analysis (using Accelerate Workflow) or customised, user-defined analysis.

CytoSure Interpret Software delivers:

- Fast, accurate and simple analysis of aCGH data
- Comprehensive data annotation with direct links to external databases and online resources
- A robust relational database allowing sophisticated data querying and filtering
- Extensive customisation options
- Fully integrated, automatic analysis of array image files

Effortless translation of oligo aCGH into meaningful results

The "Accelerate Workflow" provides automated data analysis based on predefined settings. This unique feature minimises user intervention and maximises the consistency and speed of analysis. Batch processing allows an unlimited number of samples to be analysed simultaneously with the Circular Binary Segmentation (CBS) algorithm (Figure 1). Regions of LOH are analysed with our proprietary SNP calling algorithm (Figure 2).

Direct links to external databases and online resources

CytoSure Interpret Software includes extensive annotation tracks covering syndromes, genes, exons, CNVs and segmental duplication — linked to publicly available databases such as ISCA, Decipher, Database of Genomic Variants and the Cancer Gene Census (Figure 3) providing results in context. Each track can reference hg18, hg19 or hg38 information.

Sophisticated data querying and filtering

The powerful relational database enables storage of sample data according to its relationship with other data and back-ups are straightforward with the choice of full, partial or mini back up. The database is customisable with a choice of management systems designed to integrate with your current IT infrastructure. The unique "Family Tree" viewer allows probands to be linked to other family members to view aberrations across three generations.

Designed to meet the needs of your laboratory

Complete flexibility to optimise data analysis settings and customise data reports. The permission-based log-on structure enables greater flexibility for management of user accounts.

Compatible with a variety of microarray scanners

The CytoSure Interpret Feature Extraction Module allows analysis of TIFF images from a variety of microarray scanners. The module comes pre-loaded with template files enabling images to be feature-extracted and seamlessly loaded into the Accelerate Workflow without the need for user intervention.

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CytoSure™

Figure 1: Automated aberration detection with CytoSure Interpret Software, showing clear detection of chromosomal abnormalities. The gain on chromosome 12 for this chronic lymphocytic leukaemia (CLL) sample contains the zinc finger protein gene *ZP384*, easily identified in the Cancer Gene Census genes track.

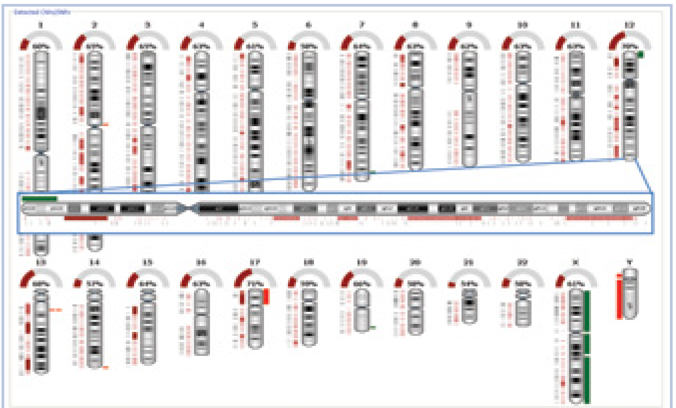


Figure 2: Automated SNP detection and LOH calling with CytoSure Interpret Software. The dark red rectangles indicate regions of LOH. The green and the bright red rectangles indicate amplifications and deletions respectively. This is the same CLL sample as displayed in Figure 1 and clearly illustrates the gain in the telomere region of the p arm and the region of LOH in p13.31-p12.3

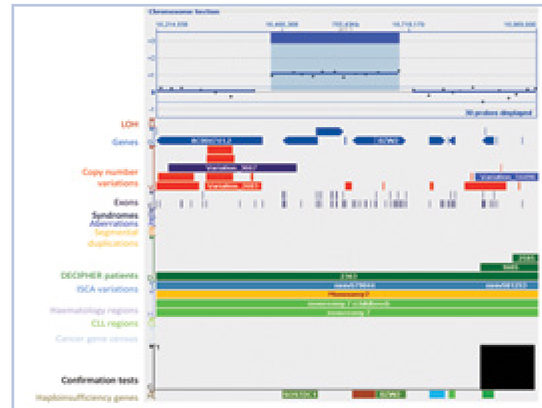
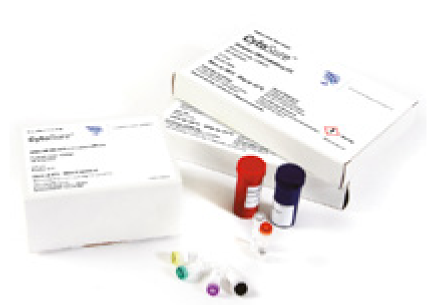


Figure 3: Fully customisable tracks simplify interpretation of aberrations.

CytoSure Genomic DNA Labelling Kits



Efficient and reproducible labelling of DNA samples for use in aCGH.

CytoSure Genomic DNA Labelling Kits deliver:

- Optimised formats to suit your throughput requirements
- Reliable high-quality results through higher signal intensity
- A fast and simple procedure

Everything you need, from reagents to plasticware

The labelling of DNA samples used in array comparative genomic hybridisation (aCGH) is a critical step in the experimental process as poor labelling can result in inaccurate data. As part of a complete labelling solution — protocols, reagents, clean-up plates or columns and collection tubes — OGT's CytoSure Genomic DNA Labelling Kits have been uniquely developed and optimised to enable rapid delivery of high-quality results with high signal-to-noise ratios.

Tested with a wide range of sample types to ensure optimal performance

Offering reliable, high-quality results, the CytoSure Genomic DNA Labelling Kits ensure superior signal-to-noise ratios for confident detection of copy number variation. This high signal-to-noise ratio means that even small aberrations can be reliably detected (Figure 1).

CytoSure Genomic DNA Labelling Kits offer much faster DNA labelling and clean up than traditional enzymatic labelling procedures. Labelling reactions using both the 24 and 96 reaction kits can easily be completed in a single day (Figure 2). The procedure can also be automated for implementation in high-throughput workflows.

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CytoSure™

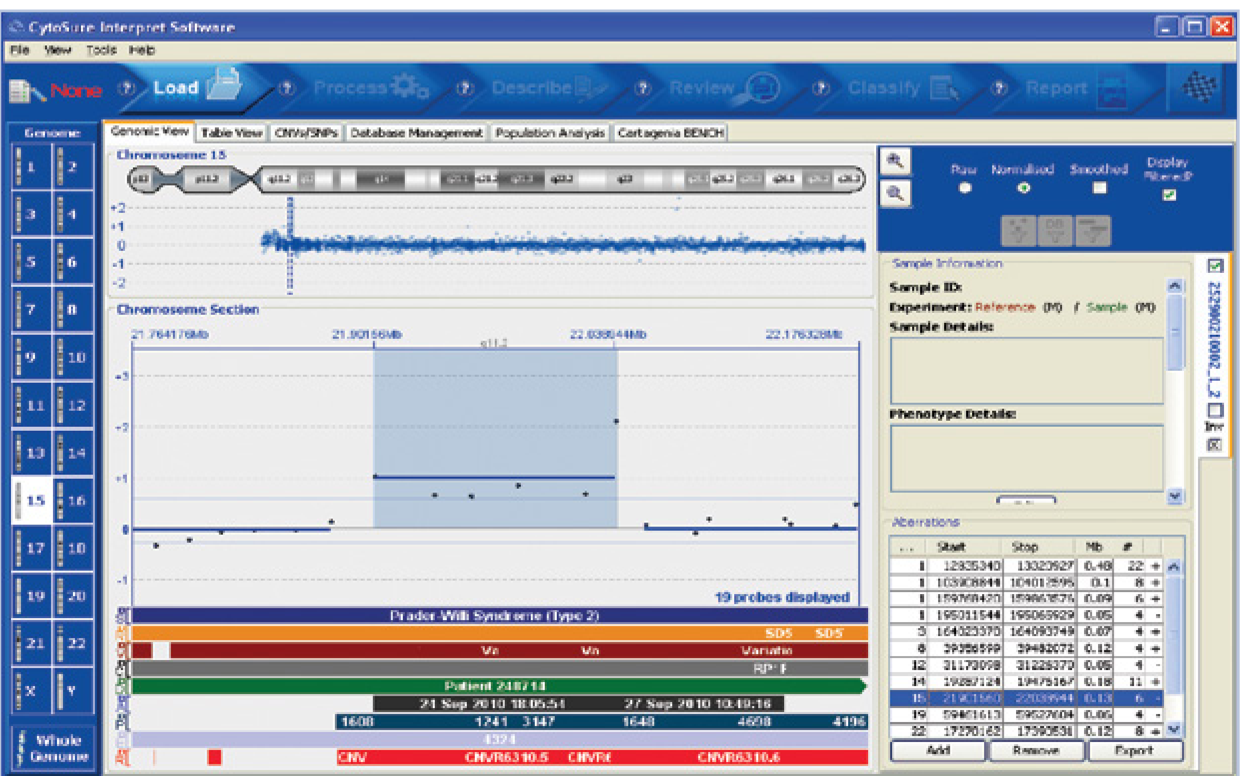

Figure 1: Reliable detection of small aberrations. DNA labelled using the CytoSure Genomic DNA Labelling Kit was run on a CytoSure ISCA 8x60K array. CytoSure Interpret Software combined with high DNA signal intensity allowed detection of a small (130 kb) DNA amplification.

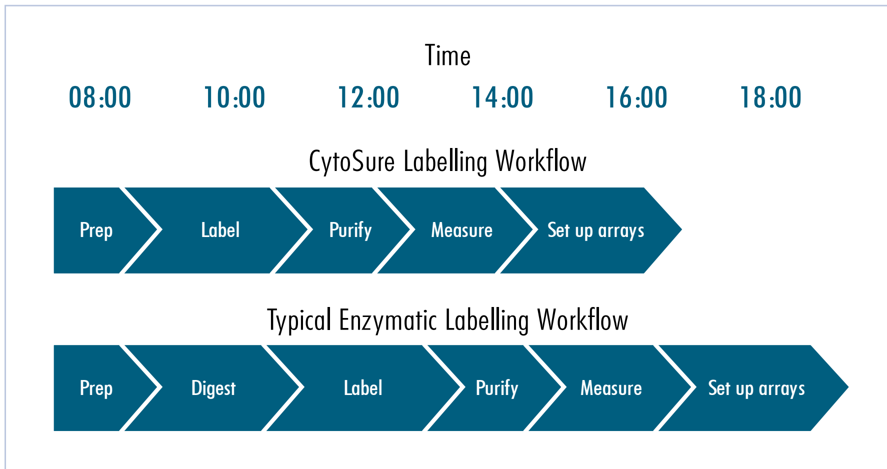

Figure 2: Two typical labelling workflows: With no need to digest, CytoSure Genomic DNA Labelling Kits save you at least 2 hours.

Product	Contents	Cat. No.
CytoSure Genomic DNA Labelling Kit	24 reactions: clean-up columns, dyes, nucleotide mix, random primers, enzyme, collection tubes	020020
CytoSure HT Genomic DNA Labelling Kit	96 reactions: 2 purification plates, nucleotide mix, random primers, enzyme	500040

CytoSure Sample Tracking Spike-ins

Reliable sample identity tracking for use with CytoSure arrays.

CytoSure Sample Tracking Spike-ins deliver:

- Confidence in results
- Simple one-step procedure with no alteration to existing workflows
- Easy identification of sample mix-up

Complete confidence in results

Increasing numbers of aCGH (array comparative genomic hybridisation) samples combined with higher-throughput array formats means that it is imperative to track samples throughout the labelling, hybridisation and analysis process to maintain sample identity. CytoSure Sample Tracking Spike-ins are uniquely designed to enable reliable sample tracking and easy identification of sample mix-up using OGT's class-leading CytoSure Arrays and CytoSure Interpret Software.

Each CytoSure Sample Tracking Spike-in is designed to a specific, unique region of the genome. Oligonucleotide probes complementary to the sample tracking spike-ins are included on all of the arrays supplied and optimised by OGT. Eight different CytoSure Sample Tracking Spike-ins are available. Each spike-in has been carefully prepared to ensure that there is no cross-hybridisation with other probes on the array or with any other region on the genome. In addition, colour-coded caps are used for ease of identification, aiding correct usage.

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Accessories

Product	Description	Cat. No.
Oligo aCGH/ChIP-on-Chip Hybridisation Kit	Hybridisation reagents for 100 samples	500013
	Hybridisation reagents for 25 samples	500014
DNA clean up plate	96 well plate for the clean up of DNA	500041
DNA clean up columns	24 columns for the clean up of DNA	500020
Wash Buffer 1 & 2 set	Buffers for post hybridisation washing of arrays – 3x 4L	500015
Backing plate (gaskets)	Backing for 8x arrays	500010
	Backing for 4x arrays	500011
	Backing for 2x arrays	500012
	Backing for 1x arrays	500017
COT Human DNA (250µl)	Blocking reagent to prevent non-specific hybridisation	500025
Human Genomic DNA, Male (100µg)	Reference DNA	500026
Human Genomic DNA, Female (100µg)	Reference DNA	500027

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Educational Resources

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Overview

Oxford Gene Technology is committed to providing comprehensive support services and resources for our products.

This new section of the catalogue is a small selection of technical resources to provide introductions, guidance for product selection, protocol overviews, and troubleshooting for your workflows.

Please read on for handy references and proven tips for FISH, NGS and arrays. Visit www.ogt.com/support for the full offering of content from our in-house experts and customers. We have application notes, posters, protocols, instructional videos and regularly updated feature pages to share the most recent advancements in the field.

www.ogt.com/support

FISH Glossary

Chromosome basics, guide to chromomaps and common terms explained

Regulatory abbreviations

IFU	Instructions For Use. May also be referred to as a pack insert.
IVD	*In Vitro* Diagnostic Medical Device. IVDs placed on the market in the European Union must be CE marked in accordance with the appropriate EU legislation.
RUO	For Research Use Only. Not for use in diagnostic procedures.
UDI	Unique Device Identification/Identifier.

Chromosome basics: Glossary of terms

Nucleus	An organelle found in eukaryotic cells that contains genetic material, deoxyribonucleic acid (DNA).
DNA	(Deoxyribonucleic acid): A self-replicating material which encodes hereditary information present in all living organisms as the main constituent of chromosomes. DNA encodes hereditary genetic information using four nucleotides; adenine, thymine, cytosine and guanine.
Chromosome	A condensed form of the highly organised structure of nucleic acids and proteins found in the nucleus of most living cells, carrying genetic information in the form of genes. Humans have 23 pairs of chromosomes.
Chromatid	One of the two threadlike strands (sister chromatids) into which a chromosome divides longitudinally during cell division.
p arm	The short arm of the chromosome (with the exception of a metacentric chromosome which has chromosome arms of equal length).
q arm	The long arm of the chromosome (with the exception of a metacentric chromosome which has chromosome arms of equal length).
Centromere	A primary constriction which separates the p arm from the q arm and holds the pair of sister chromatids together. A region of α satellite DNA sequences. The centromere is the point at which the chromosome is attached to the spindle during cell division.
Telomere	A compound structure at the end(s) of a chromosome, consisting of repetitive nucleotide sequences.
Gene	A unit of heredity which is transferred from a parent to offspring and is known to determine some characteristics of the offspring. A gene consists of a sequence of nucleotides in DNA that encode the synthesis of a gene product, such as a protein or RNA molecule.

Anatomy of a chromosome

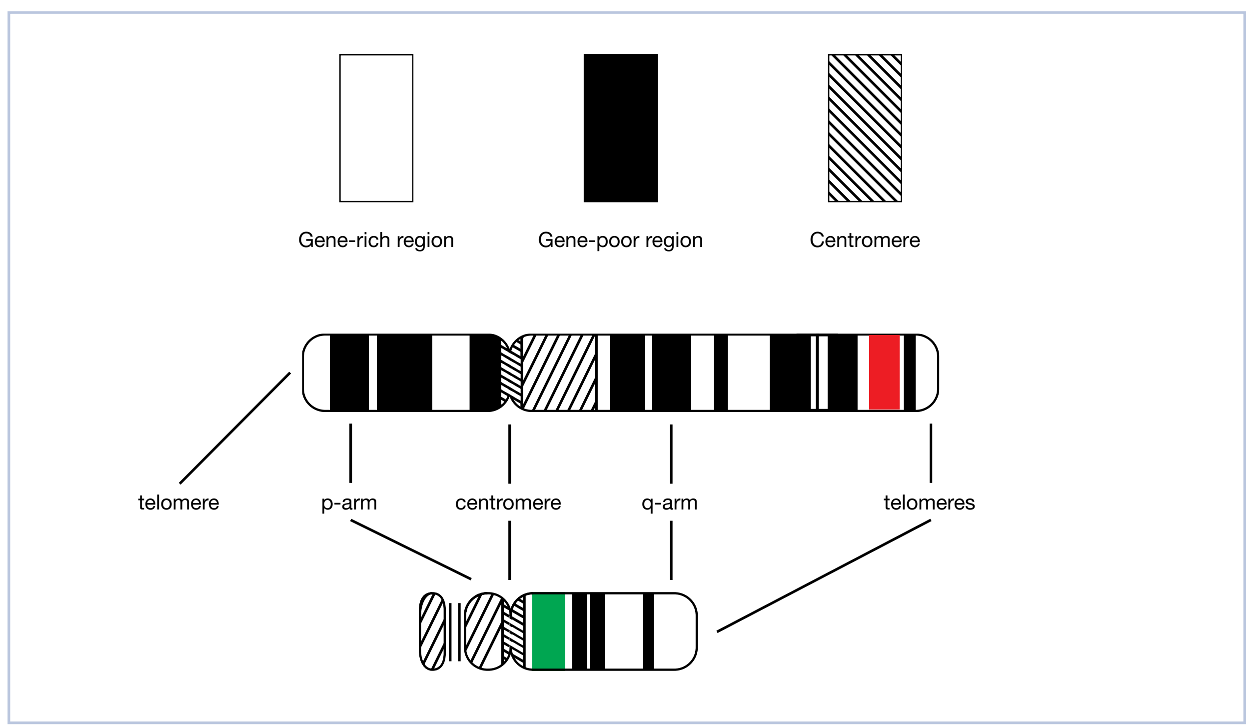


Figure 1: Characteristic banding pattern produced by exposure to trypsin during G banding. G band light regions tend to be gene rich. G band dark regions tend to be gene poor. Giemsa banding is a technique used in cytogenetics to produce a visible karyotype by staining condensed chromosomes

Types of chromosome arm

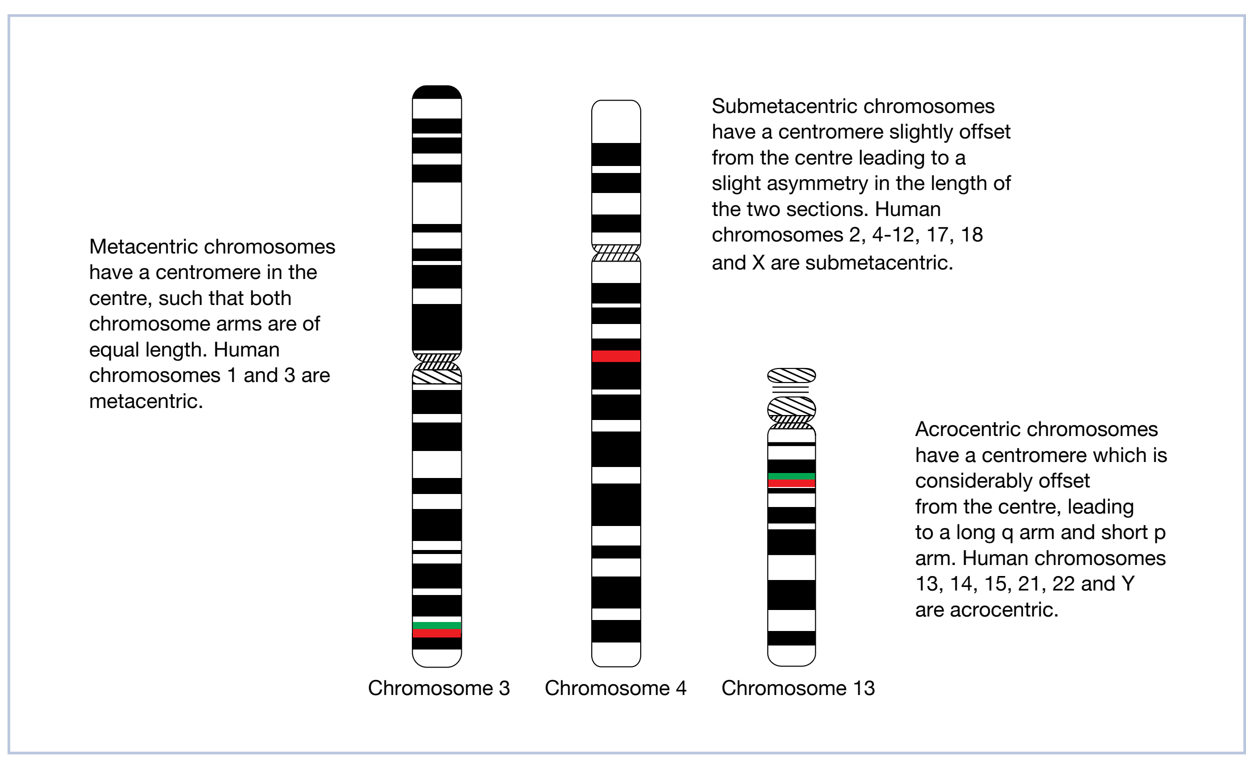


Figure 2: Metacentric (left), submetacentric (centre) and acrocentric (right) chromosomes

Probe maps and gene orientation

Probe maps in the OGT Product Catalogue, Second Edition, have been updated to include information on gene orientation to allow the 3' or 5' positions of the probes to be seen in relation to the gene, or region, of interest. The arrows on the genes indicate the direction of transcription. Those with an arrow above, pointing to the right, are located on the plus, or sense, strand of the DNA. Those with an arrow below the gene, pointing to the left, are on the minus, antisense strand. In both cases, the 5' end is that with the arrow as genes are transcribed in a 5' to 3' direction. Examples can be seen below.

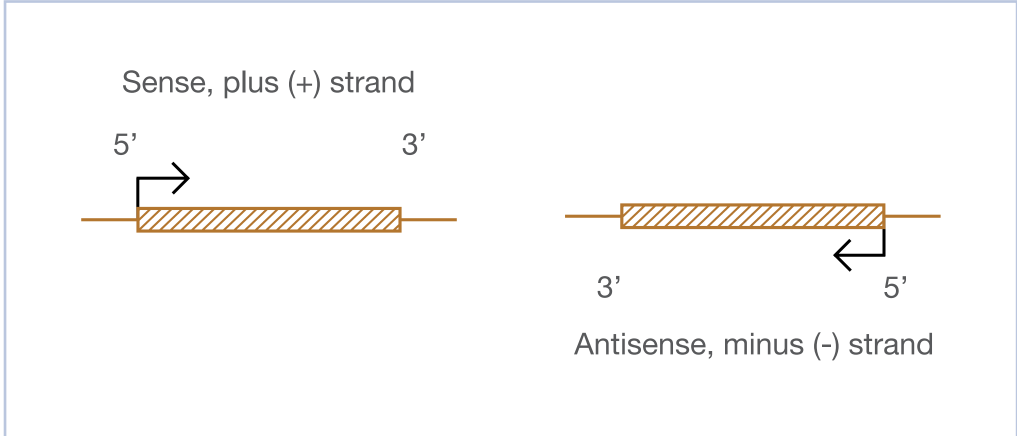


Figure 3: Arrows on genes in chromomaps indicate the direction of transcription.

HGNC Nomenclature

Gene names have also been updated to reflect current HUGO Gene Nomenclature Committee (HGNC) approved symbols. Where this affects existing product names, the approved HGNC symbol is placed into brackets. All gene names were checked and updated according to the HGNC database[1] as of April 2019.

1. HGNC Database, HUGO Gene Nomenclature Committee (HGNC), EMBL Outstation - Hinxton, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SD, UK. www.genenames.org

Types of probes

In theory, any region of a chromosome can be a target for a FISH probe. Cytocell probes may label chromosomes anywhere along the p or q arm: the subtelomere, the centromere, or any specific gene region in between.

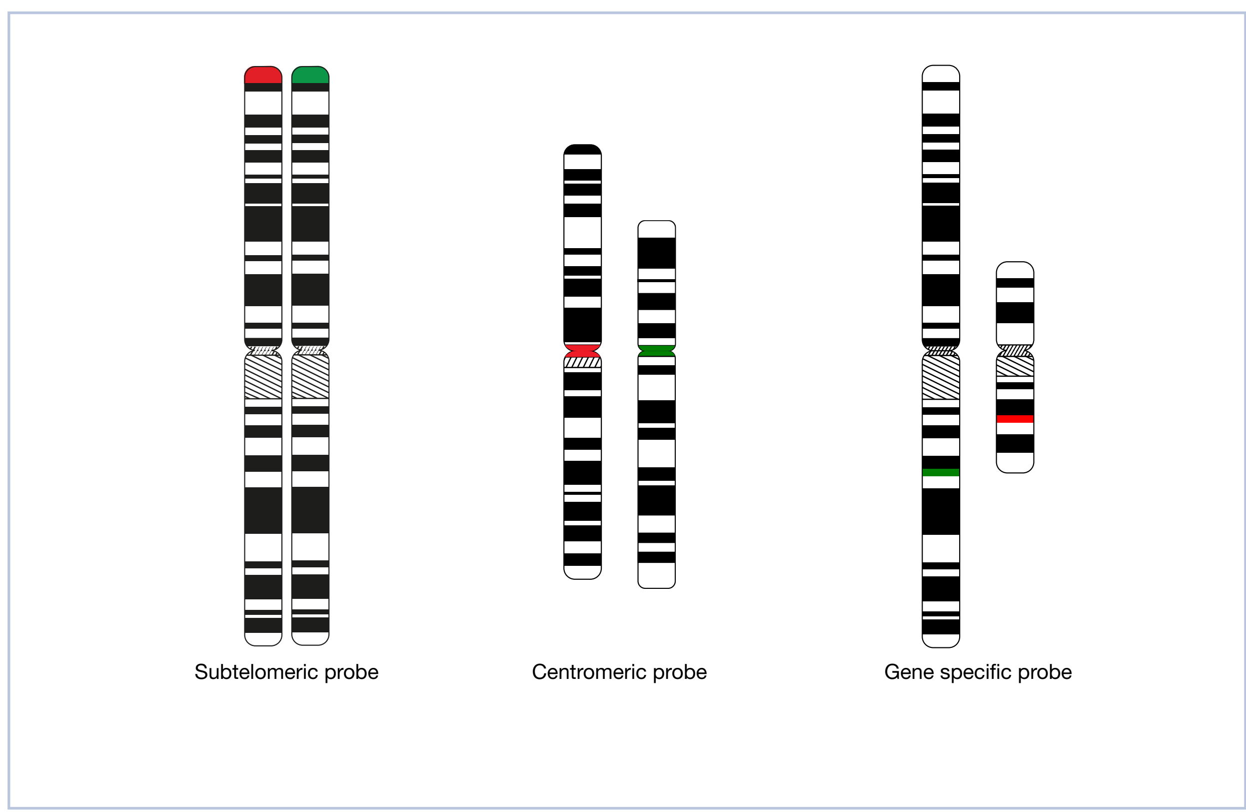
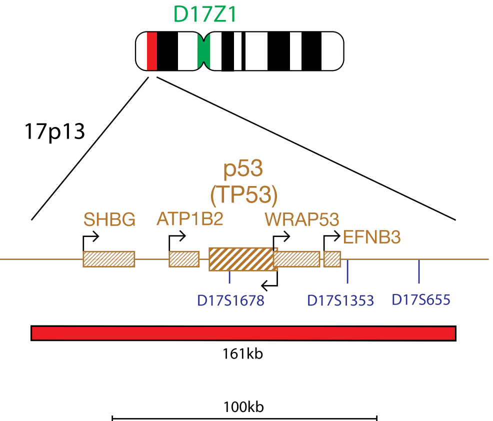


Figure 4: Illustration of Cytocell subtelomeric, centromeric and gene specific FISH probes.

Probe design

An example of the convention at OGT for assignment of a fluorophore* can be viewed with the P53 (TP53) Deletion probe (LPH 017):

- Green = control
- Red = target region of interest



* There are some exceptions to this convention, please consult the IFU for probe map and full details.

Probe nomenclature explained

Using the TLX1 Breakapart (LPH 049) probe as an example:

TLX1 Breakapart

Breakapart = Probe design / signal pattern, one fluorophore for 3' end and a different colour fluorophore for 5' end

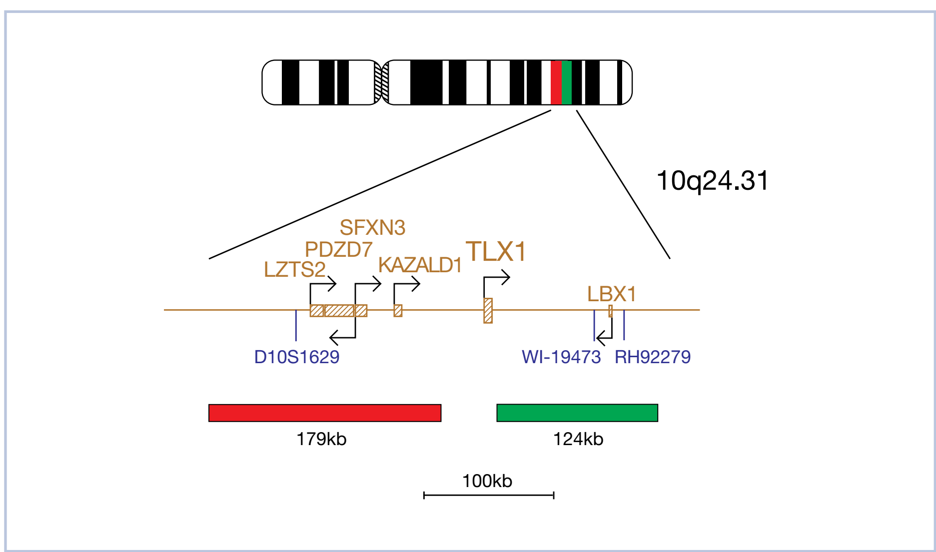


Figure 5: Cytocell chromomap for TLX1 Breakapart.

Guide to Chromosome Region

10q24.31 =

Chromosome 10 / q arm / Band 24 / Sub-band 31

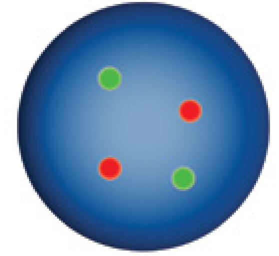
Cytocell catalogue product numbers explained:

LPH	Haematology probes.
LPS	Solid tumour and haematopathology probes. Optimised for formalin fixed paraffin embedded (FFPE) tissue. It is more difficult for the probe to reach the target DNA in FFPE tissue, so pre-treatment steps are required.
LPD	Dual use probes. Optimised for both peripheral blood/bone marrow and FFPE tissue.
LPE	Chromosome enumeration probes.
LPU	Microdeletion probes.
LPT	Subtelomeric probes.

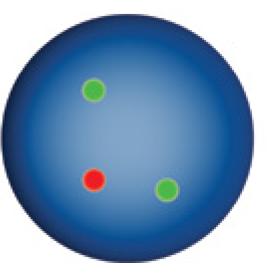
Common FISH Signal Patterns

Deletion Probe Signal Patterns

Expected Normal Signal Pattern

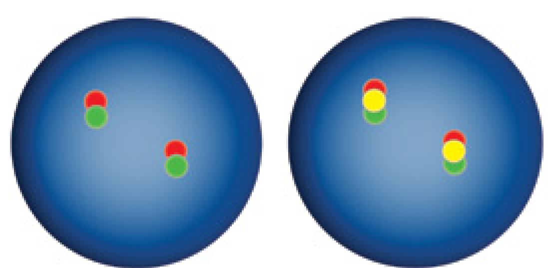


Abnormal Deletion Signal Pattern

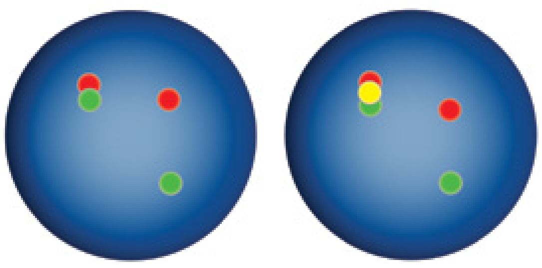


Breakapart Probe Signal Patterns

Expected Normal Signal Pattern



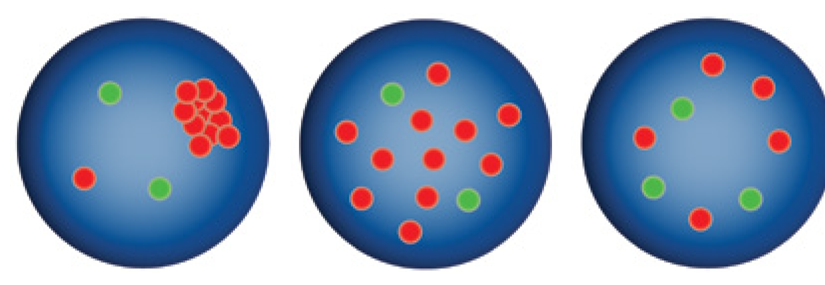
Abnormal Breakapart Signal Patterns



Amplification Probe Signal Patterns

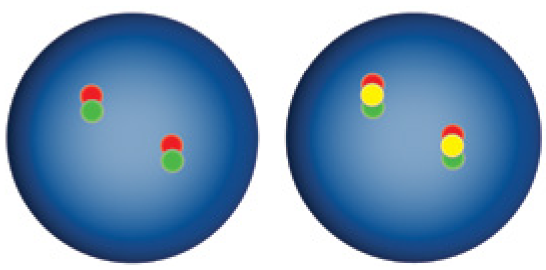
Expected Normal Signal Pattern

Abnormal Amplification Signal Patterns

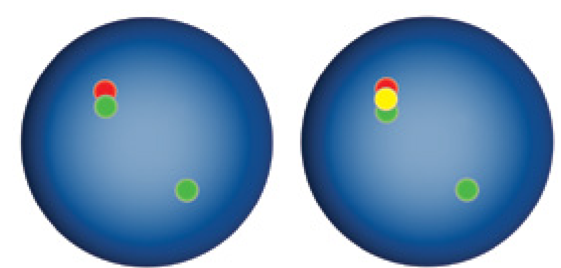


Deletion/Fusion Probe Signal Patterns

Expected Normal Signal Patterns

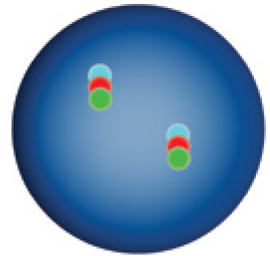


Abnormal Deletion/Fusion Signal Patterns

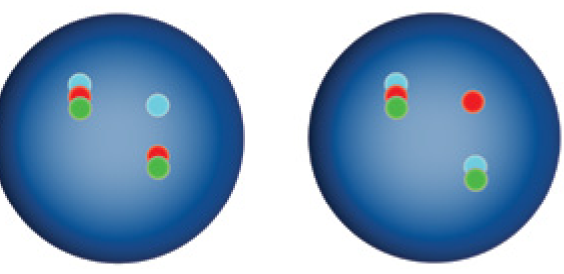


3-Colour Breakapart Probe Signal Patterns

Expected Normal Signal Pattern

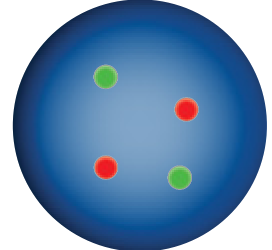


Abnormal 3 Colour Breakapart Signal Pattern

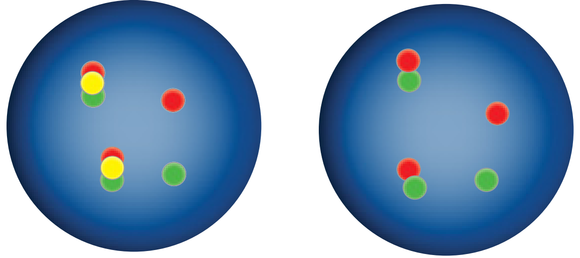


Translocation, Dual Fusion Probe Signal Patterns

Expected Normal Signal Pattern



Abnormal Translocation, Dual Fusion Signal Patterns



Recommended protocols for Cytocell Aquarius® FISH probes

Recommended protocols for: 1) Cytocell Haematology FISH and 2) FFPE Tissue Preparation and Cytocell Pathology FISH. Reference the Instructions for Use (IFU) for warnings, precautions, storage, and handling.

Study the IFU carefully before using this quick reference guide. The IFU can be found in the product packaging and by using the Resources section of the Cytocell website (www.cytocell.com/resources)

Note: This quick reference guide does not replace the content from the IFU.

Overview

Fluorescence *in situ* hybridisation (FISH) is a technique that allows DNA sequences to be detected on metaphase chromosomes or in interphase nuclei from fixed cytogenetic samples. The technique uses DNA probes that hybridise to entire chromosomes or single unique sequences, and serves as a powerful adjunct to classic cytogenetics. This valuable technique can now be applied as an essential diagnostic tool in prenatal, haematological and pathological chromosomal analysis. Target DNA, after fixation and denaturation, is available for annealing to a similarly denatured, fluorescently labelled DNA probe, which has a complementary sequence.

Following hybridisation, unbound and non-specifically bound DNA probe is removed and the DNA is counterstained for visualisation. Fluorescence microscopy then allows the visualisation of the hybridised probe on the target material.

Materials Provided

The FISH probes are provided in a ready-to-use format and premixed with hybridisation solution (formamide; dextran sulfate; saline-sodium citrate (SSC)). In addition a 150µl vial of ready-to-use DAPI counterstain with antifade (0.125µg/ml DAPI (4,6-diamidino-2-phenylindole)) is provided. See the IFU for additional details.

Cytocell Haematology and Pathology FISH Probe Kits are not intended for: use as a stand-alone diagnostic, prenatal testing, population-based screening, near-patient testing, or self-testing.

Cytocell FISH Probe Kits are intended for laboratory professional use only.

Cytocell FISH Probe Kits have not been validated for sample types, disease types, or purposes outside of those stated in the intended use.

Cytocell FISH Probe Kits are intended as an adjunct to other diagnostic laboratory tests and therapeutic action should not be initiated on the basis of the FISH result alone.

Reporting and interpretation of FISH results should be performed by suitably qualified staff, consistent with professional standards of practice, and should take into consideration other relevant test results, clinical and diagnostic information.

Failure to adhere to the protocol may affect the performance and lead to false positive/negative results.

Please refer to the IFU for more detailed information. This can be found in the product packaging and by using the Resources section of the Cytocell website.

IVD: *In Vitro* Diagnostic Medical Device

Product availability may vary from country to country and is subject to varying regulatory requirements.

Recommended protocol for Cytocell Haematology FISH

Example protocol to perform fluoresence *in situ* hybridisation (FISH) using Cytocell haematology FISH probes.

Step 1

Sample and slide preparation

- Spot the cell sample onto a glass microscope slide. Allow to dry.
- Immerse the slide in 2x Saline Sodium Citrate (SSC) for 2 minutes at room temperature (RT) without agitation.
- Dehydrate in an ethanol series (70%, 85% and 100%), each for 2 minutes at RT.
- Allow to dry.

Step 2

Pre-denaturation

- Remove the probe from the freezer and allow it to warm to RT. Briefly centrifuge tubes before use.
- Ensure that the probe solution is sufficiently mixed with a pipette or a vortex mixer.
- Remove 10µl of probe per test, and transfer it to a microcentrifuge tube. Quickly return the remaining probe to -20ºC.
- Place the probe and the sample slide to prewarm on a 37ºC (+/- 1ºC) hotplate for 5 minutes.
- Spot 10µl of probe mixture onto the cell sample and carefully apply a 24x24mm coverslip. Seal with rubber solution glue and allow the glue to dry completely.

Step 3

Denaturation

- Denature the sample and probe simultaneously by heating the slide on a hotplate at 75ºC (+/- 1ºC) for 2 minutes.

Step 4

Hybridisation

- Place the slide in a humid, lightproof container at 37ºC (+/- 1ºC) overnight.

Step 5

Post-hybridisation washes

- Remove the DAPI from the freezer and allow it to warm to RT.
- Remove the coverslip and all traces of glue carefully.
- Immerse the slide in 0.4x Saline Sodium Citrate (SSC) (pH 7.0) at 72ºC (+/- 1ºC) for 2 minutes without agitation.
- Drain the slide and immerse it in 2xSSC + 0.05% Tween-20 at RT (pH 7.0) for 30 seconds without agitation.
- Drain the slide and apply 10µl of DAPI antifade onto each sample.
- Cover with a 24x24mm coverslip, remove any bubbles.
- Edge the slide with clear nail varnish to seal.
- Allow the color to develop in the dark for 10 minutes.

Step 6

Analyse

- View with a fluorescence microscope.
- For optimal visualisation of the probes, a 100-Watt mercury lamp (or equivalent) is recommended with plan apochromat objectives 63x or 100x.
- Filters designed specifically for detection of DAPI, FITC, Texas Red®, and Aqua or DEAC fluorophores individually or in combination (e.g. dual or triple filters) are optimal for best results.
- The final hybridised slides are analysable for up to 1 month when stored in darkness and at 2-8°C.

FFPE Tissue preparation and FISH protocol

Slide preparation

For FISH, 4μm - 6μm thick FFPE tissue sections should be used. Slides should be treated with an adhesive before mounting tissue section. Throughout the entire procedure, unless otherwise indicated, it is important that the tissue section does not dehydrate. For optimal results, use the Aquarius Tissue Pretreatment Kit (LPS 100).

Step 1

Heat Pretreatment

- Heat 500ml Tissue Pretreatment Solution (Reagent 1) until it is either boiling or 96-98°C.
- Heat slides for 15 minutes (Note: different incubation times may be required depending on tissue fixation. A 15 minute incubation is a recommended starting point).
- Wash in PBS or dH_2O at room temperature (RT) for 2 x 3 minutes.

Step 2

Enzyme Digestion

- Cover tissue with 100-200μl of Enzyme Reagent (Reagent 2) for 10 minutes at RT.
  Note: depending on tissue fixative used, different incubation times may be required. Excessive digestion will cause loss of nuclei and chromosome structure.
- Wash in PBS or dH_2O at RT for 3 x 2 minutes.
- Dehydrate slides in a series of 70%, 85%, 95% and 100% ethanol for 2 minutes each at room temperature, air dry, and proceed to denaturation and hybridization.

Step 3

Pre-Denaturation

- Remove the probe from the freezer and allow it to warm to room temperature (RT).
- Ensure that the probe solution is uniformly mixed with a pipette.
- Remove 10μl - 15μl (depending on the size of the tissue) of probe per test, and transfer it to a microcentrifuge tube. Quickly return the remaining probe to -20ºC.
- Place the probe and the sample slide to prewarm on a 37ºC (+/- 1ºC) hotplate for 5 minutes.
- Spot 10μl - 15μl of probe mixture onto the sample and carefully apply a coverslip. Seal with rubber solution glue and allow the glue to dry completely.

Step 4

Denaturation

- Denature the sample and probe simultaneously by heating the slide on a hotplate at 75ºC (+/- 1ºC) for 5 minutes.

Step 5

Hybridisation

- Place the slide in a humid, lightproof container at 37ºC (+/- 1ºC) overnight.

Step 6

Post-hybridisation washes

- Remove the coverslip and all traces of glue carefully.
- Immerse the slide in 0.4xSSC (pH 7.0) at 72ºC (+/- 1ºC) for 2 minutes without agitation.
- Drain the slide and immerse it in 2xSSC, 0.05% Tween-20 at RT (pH 7.0) for 30 seconds without agitation.
- Drain the slide and apply 10μl - 15μl of DAPI antifade onto each sample.
- Cover with a coverslip, remove any bubbles and allow the colour to develop in the dark for 10 minutes.

Step 7

Analyse

- View with a fluorescence microscope.

Comments

Hybridisation efficiency and tissue morphology are usually negatively correlated. Aggressive pretreatment procedures which improve hybridisation efficiency (e.g. an extended enzyme digestion time) tend to destroy cell structure and tissue morphology. However, mild pretreatment which saves tissue structures may not be sufficient for probe penetration and successful FISH results.

The optimal length of heat pretreatment and enzyme digestion time will depend on the age of the block, the tissue composition, and quality of tissue fixation. Enzyme digestion should be decreased for core biopsies and any sections that contain few tumour cells or have large areas of necrosis. These samples need to be handled particularly carefully to avoid over-digestion.

Troubleshooting

- **Heat Pretreatment (the most critical step for successful performance):** The specimen must be heated at 96-98°C for 15 minutes in Heat Pretreatment Solution.
- **Enzyme Digestion (a critical step for successful performance):** Different enzyme incubation times (5 - 15 minutes) may be required, depending on tissue type and fixation method. For most breast tissues, 10 minutes enzyme digestion at RT will produce the best results. Be sure to pre-warm the Enzyme Pretreatment Reagent to RT prior to adding to the tissue section. Enzyme pretreatment of the specimen should be evaluated immediately at the completion of the protocol. If nuclei are not counterstained and there is an absent or very weak signal, this may be due to nuclear loss as the result of excessive digestion. If nuclei are strongly counterstained but a signal is absent in the nuclei, this may be due to under-digestion during the pepsin pretreatment. As an alternative, enzyme pretreatment may also be performed at 37°C for 3 - 10 minutes if optimal results are not attained.
- **Probe denaturation at a temperature lower than recommended by the protocol may result in a weak or absent signal.**
- **Hybridisation performed for shorter time periods, or stringent washes performed at higher temperatures, than recommended by the protocol may produce a decrease in or complete loss of the signal.**

Next Generation Sequencing

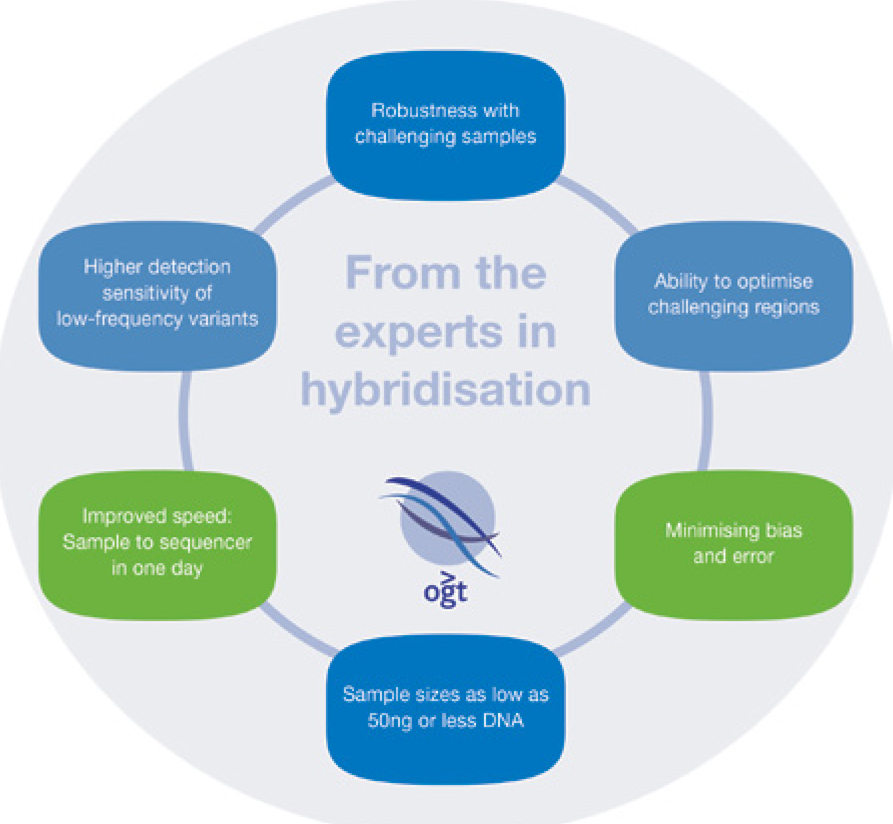
Choosing the best enrichment assay

Next generation sequencing (NGS) is now in routine use for a broad range of research and clinical applications. The rapid rate of adoption has been facilitated by falling reagent costs, benchtop instruments, improved chemistries and improved data analysis solutions. However, the cost and complexity of data analysis still remain significant hurdles — particularly for whole genome sequencing. In the majority of cases, targeted approaches, such as custom NGS panels, are more cost-effective and generate significantly less, but equally meaningful data in a much shorter timescale.

Targeted sequencing requires an initial sequence enrichment step, which, if poorly designed, can be a source of bias and error in the downstream sequencing assay[1].

Which enrichment assay?

Two broad categories of enrichment assays exist: amplicon (PCR) and hybridisation. As a very general rule, hybridisation-based assays, when designed well, offer superior performance[2]. Please see the following pages for an overview detailing hybrisisation vs. amplicon. Additional information and a downloadable whitepaper can be found online at www.ogt.com/enrichment



REFERENCES

1. Aird, D. *et al* (2011) Analyzing and minimizing PCR amplification bias in Illumina sequencing libraries. Genome Biology 12:R18 doi:10.1186/gb-2011-12-2-r18
2. Samorodnitsky, E. *et al* (2015) Evaluation of hybridization capture versus amplicon-based methods for whole-exome sequencing. Hum Mutat 36(9), 903-915

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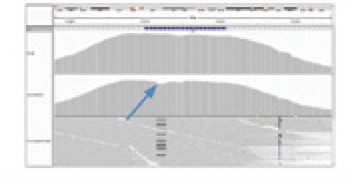
Hybridisation vs. Amplicon Enrichment

Higher detection sensitivity of low-frequency variants

Uniformity of enrichment means that all regions are represented more equally, and that variants present in any region will be called. It also allows much lower average sequencing depths to be used, enabling larger numbers of samples to be multiplexed in a run, and significant cost savings.

Reliable detection of low frequency mutations

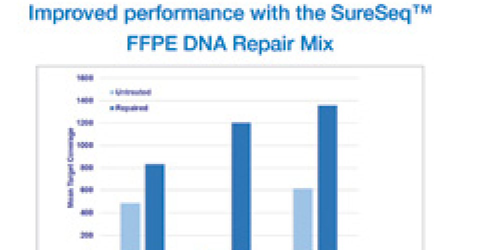


High uniformity of coverage allows the reliable detection of low frequency somatic indels even in FFPE derived DNA. Example is of a 12 bp deletion (c.754_765delCTCACCCATCATC) in exon 3 of *TP53*, 6% frequency, using the SureSeq Ovarian Cancer Panel.

Robustness with challenging samples

Unlike amplicon-based assays, hybridisation is less susceptible to contaminants found in FFPE-derived DNA. Use of an upstream FFPE repair step can significantly improve mean target coverage.

Improved performance with the SureSeq™ FFPE DNA Repair Mix

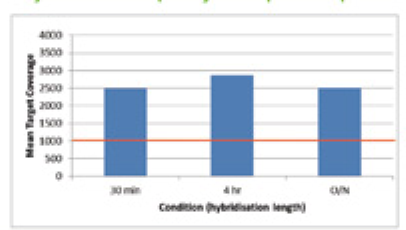


The SureSeq FFPE DNA Repair Mix significantly improves mean target coverage resulting in more confident calls.

Improved speed: Sample to sequencer in one day

With a short enzymatic fragmentation step, combined end-repair and adaptor ligation steps, and optimised hybridisation in as little as 30 minutes, you can go from sample to sequencer in a single day.

Hybridisation quality – Amplicon speed

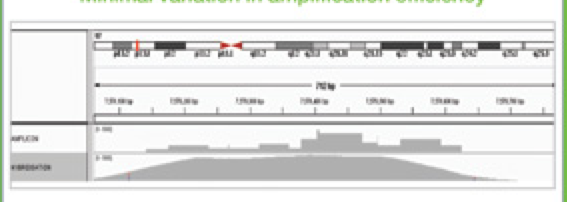


The hybridisation step has been optimised to take as little as 30 minutes with good quality DNA, without compromising results.

Minimising bias and error

Hybridisation-based assays avoid the tendency towards bias and error seen with amplicon methods as the degree of multiplexing and number of PCR cycles increases.

Minimal variation in amplification efficiency



Comparison of amplicon and hybridisation-based enrichment of the GC-rich exons 4 and 5 of the *TP53* gene illustrating the superior coverage uniformity.

Sample sizes as low as 50ng or less

Hybridisation has moved on. Well-designed hybridisation assays can now utilise lower amounts of input DNA, whilst still producing clean, bias-free, high quality data.

Confident detection with low DNA input

Effect of reduced amount of DNA input on mean target coverage and %OTR.

Ability to optimise challenging regions

OGT's innovative bait-design delivers uniform and complete coverage of difficult-to-sequence GC rich regions of the genome.

Outstanding coverage uniformity

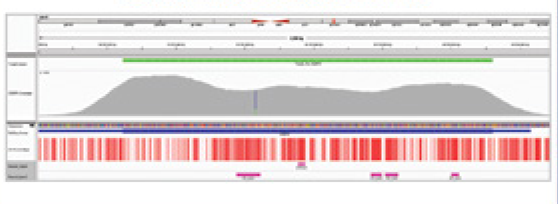


Illustration of the excellent uniformity of coverage of the *CEBPA* gene. Depth of coverage per base (grey). Targeted region (green). Gene coding region as defined by RefSeq (blue). GC percentage (red). Repeat regions (pink).

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One day hybridisation protocol for SureSeq NGS

The application of a one-day hybridisation-based enrichment protocol incorporating a rapid (30 minute) hybridisation step

Hybridisation-based enrichment protocols for next-generation sequencing (NGS) generate higher quality data (e.g. enhanced coverage uniformity, more complete coverage, and more accurate assessment of insertions/deletions (indels) and internal tandem duplications (ITDs)). However, they are generally more time consuming than PCR-based enrichment approaches. OGT has developed a rapid (30 minute) hybridisation protocol that enables Illumina sequencer-ready libraries to be generated from purified DNA in 1-day.

This enhanced version of the SureSeq™ library preparation protocol incorporates an enzymatic DNA fragmentation in combination with a rapid hybridisation of just 30 minutes. This enhanced protocol reduces the overall processing time by 6 hours, resulting in a streamlined, 1-day workflow. It offers a similar turn-around time to amplicon-based enrichment protocols, without the associated disadvantages, such as PCR bias, allelic bias (indels) and drop-outs, as well as poor uniformity of coverage.

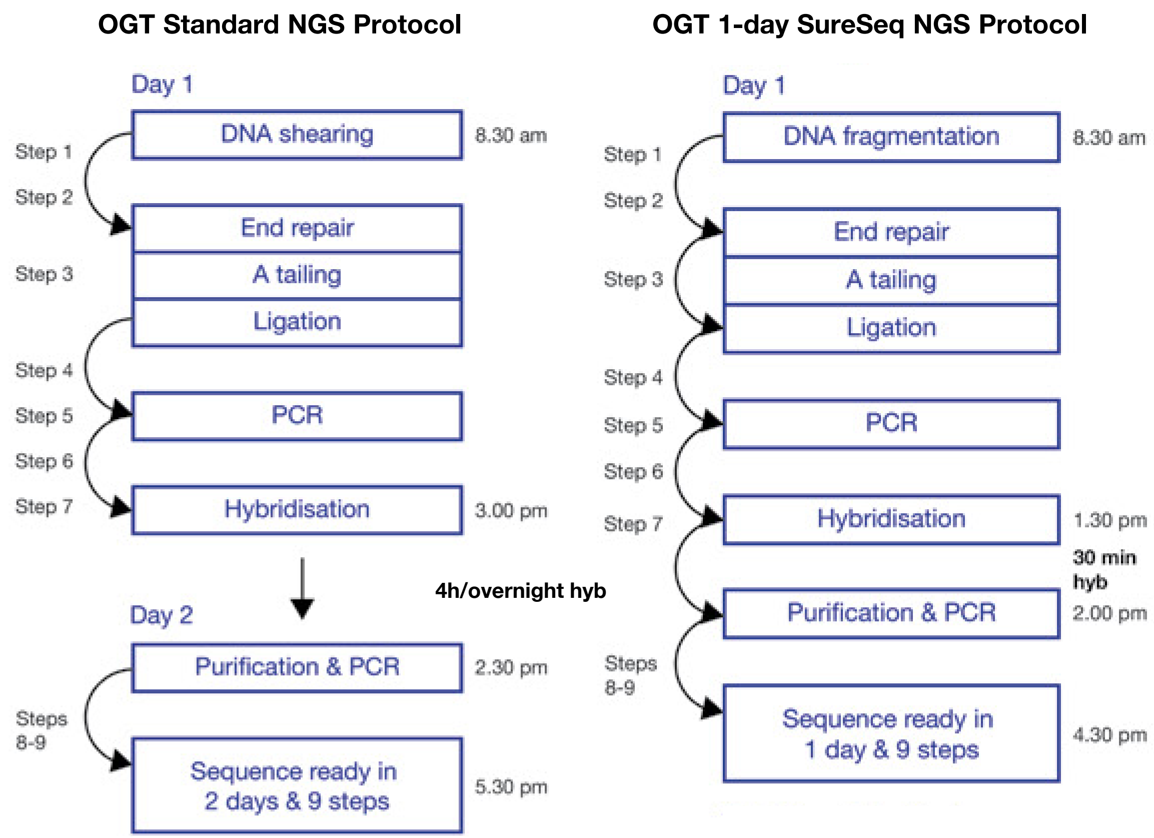

Figure 1: Comparison of workflows

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Comparison of the data generated by the 1-day and standard NGS protocols

- Four different haematological panels have been used, with a size range from 0.5 Kb to 138 Kb.
- Data presented here are from 24* samples that were processed using the enhanced LPK in combination with four haematological panels on an Illumina MiSeq.
- The quality of the data generated with the 1-day protocol is comparable to the standard 4-hour hybridisation protocol.
- OGT 1-day protocol generated >85% of the % on-target bases generated with the standard protocol. The % change is consistent for all panel sizes.

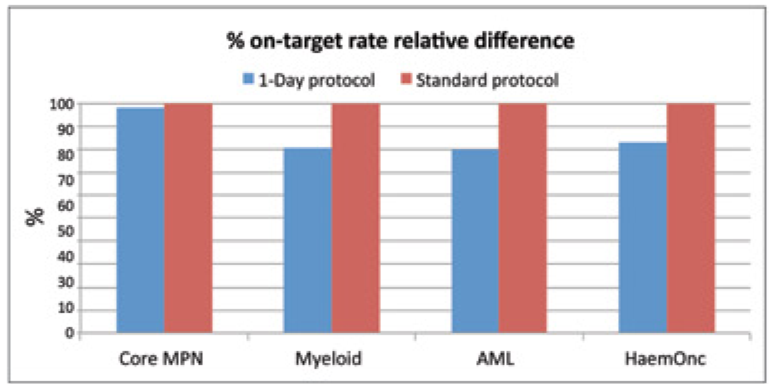

Figure 2: On-target rate comparison between 1-day and standard NGS protocol.

The MTC generated is dependent on the size of each panel. Overall, both workflows generated very good coverage. The MTC generated with the 1-day protocol is >80% of the MTC generated with the standard protocol. The % change is consistent for all panels.

All panels meet the following uniformity specifications: >99% of bases covered at >20% of the mean (after de-duplication). This permits the reliable detection of more complex rearrangements (i.e.) indels and ITDs.

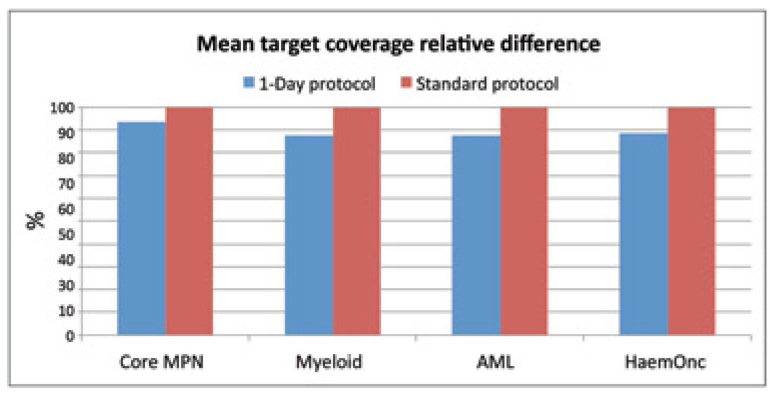

Figure 3: Mean target coverage comparison between 1-day and standard NGS protocol.

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Accurate detection of difficult to sequence genes

Mutations in the CEBPA and FLT3 genes are among the most common molecular alterations in AML. Sequencing of the CEBPA gene is often hampered by a repetitive nucleotide sequence and a very high GC-rich content. Genes such as FLT3 ITDs are challenging to target because they are by nature repetitive, can be long and are generally masked in most panel designs.

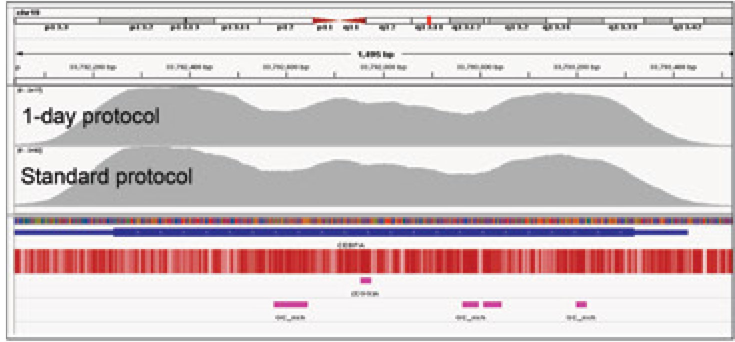


Figure 4: Excellent uniformity of coverage of the CEBPA gene averaging ~2000x coverage. Depth of coverage per base (grey). GC percentage (red). Repeat regions and GC-rich regions (pink). Data shown from 1-day protocol.

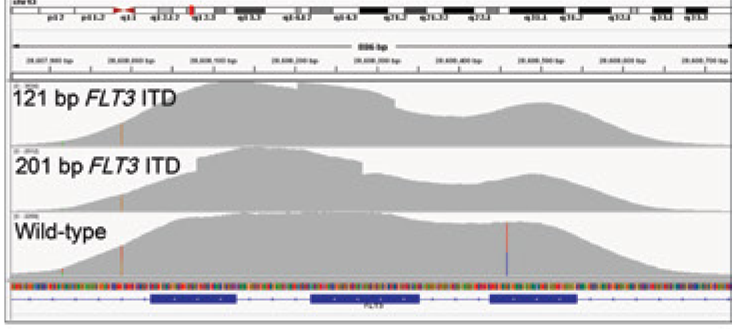


Figure 5: Detection of 121 bp and 201 bp FLT3 ITD. Wild-type sample (bottom panel).

Conclusions

- We have successfully utilised the OGT 1-day hybridisation-based SureSeq LPK protocol in combination with four haematological cancer panels to reliably and routinely detect somatic SNVs by NGS down to a 1% VAF.
- The uniformity of coverage of this approach permitted the detection of key CALR and JAK2 indels (including 52 bp deletions and 5 bp insertions) and FLT3 ITDs to be identified.
- This enhanced protocol incorporates an enzymatic fragmentation step which permits the high throughput preparation of 24-48 samples (panel size dependent) from genomic DNA to sequencer in a 1-day workflow.
- To achieve >1000x de-duplicated depth (required for confident detection of 1% VAF), 24-48 samples (panel size dependent) can be reliably sequenced in a single MiSeq (V2 300 bp) run. This allows the generation of high quality data in a cost effective and timely manner.

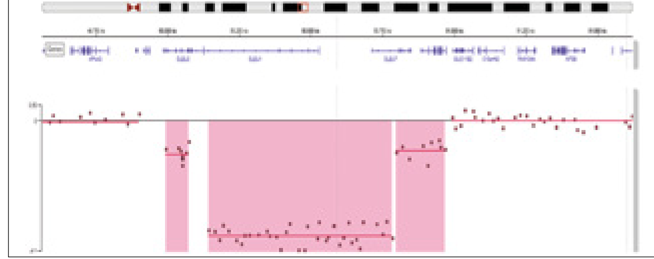
SureSeq: For Research Use Only; Not for use in diagnostic procedures.
* Samples kindly provided by Prof. Nick Cross, (National Genetics Reference Laboratories - Wessex, UK)

Comprehensive results from a single NGS assay: panel and software highlights

Streamline your research and alleviate the burden of running multiple assays

Investigating both structural aberrations and SNVs/indels is imperative to advance research into progression and treatment of various diseases. For example, copy-number variations (CNVs) are common in Chronic lymphocytic leukaemia (CLL) and the BCR-ABL fusion gene is a hallmark of Chronic Myeloid Leukaemia (CML). Facilitated by OGT's excellent bait design and Intepret software, SureSeq panels can reliably detect copy-number variations, including trisomies, and translocations; for a more comprehensive understanding of the genetic makeup of each sample - using a single NGS assay.

NGS



Array

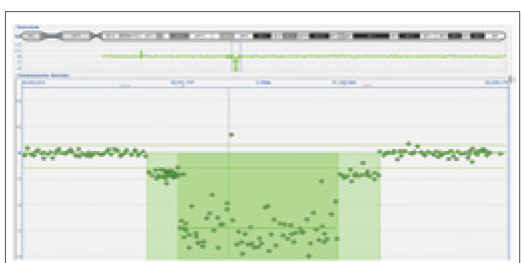


Figure 1: SureSeq CLL + CNV Panel: 0.6Mb biallelic loss called within a larger ~1Mb single allele deletion in the region covering *DLEU2/DLEU1/DLEU7* on chromosome 13q, fully concordant with array data.

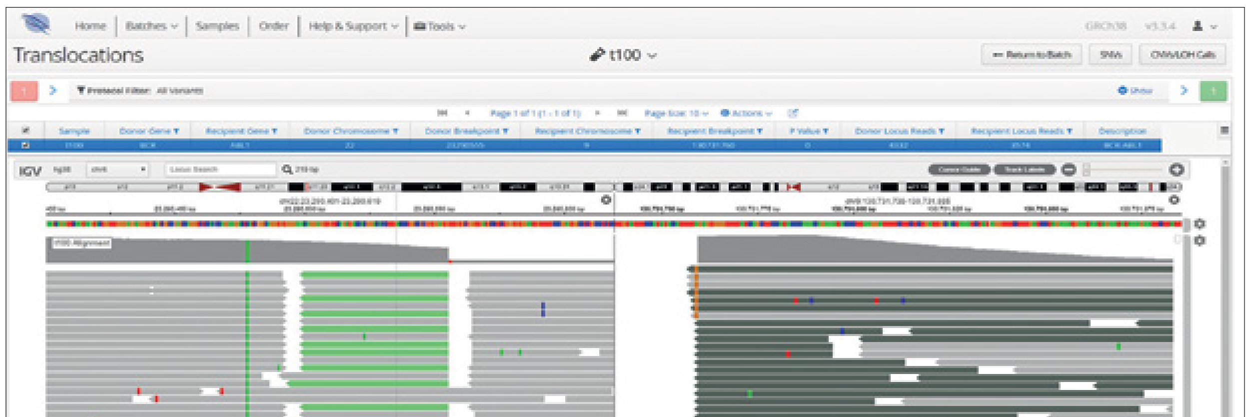


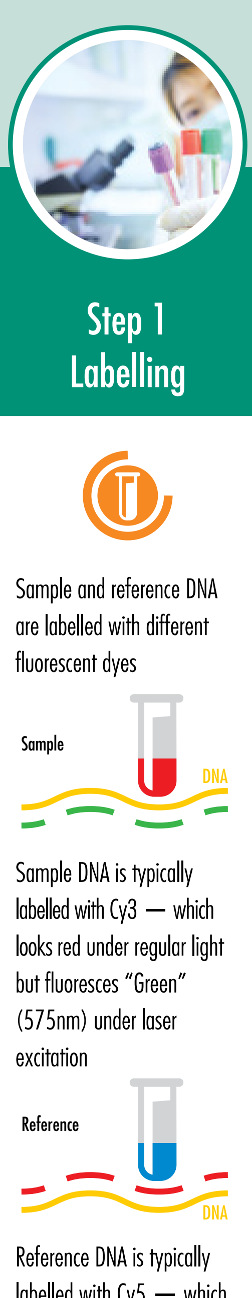
Figure 2: *BCR-ABL* translocation reported in Interpret. Split-reads covering both *BCR* (left panel) and *ABL1* (right panel) are detected, indicative of the *BCR-ABL* gene fusion.

CytoSure™

Basics of array comparative hybridisation (aCGH)

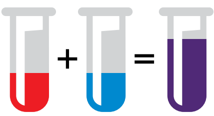
Array comparative genomic hybridisation (aCGH) is a powerful tool for analysis of CNV and LOH and is used in a multitude of different applications. CytoSure oligo aCGH products leverage OGT's expert probe design to enable superior CNV resolution to other platforms, detecting microdeletions and microduplications at exon-level resolution across a wide range of disorders.

This illustration provides the basics of how aCGH works and the steps involved. For more information, please visit: **www.ogt.com/arrays**



Step 2 Preparation

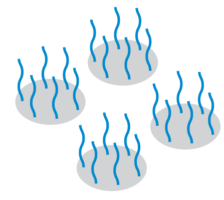
Samples are mixed into a single tube



The mixture is pipetted onto a "gasket" slide with chambers which hold the solution

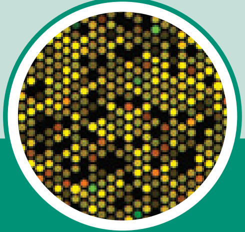
The microarray slide is then held in place against this, ready for hybridisation

Step 3 Hybridisation



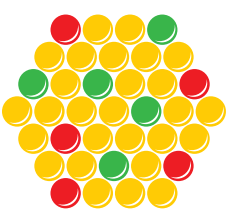
Microarrays contain tightly packed "spots" of DNA oligos, also referred to as probes. Each spot is usually designed to target a different region of the genome

Both the sample and reference labelled DNA compete to bind to the probes, in a process known as "competitive hybridisation"

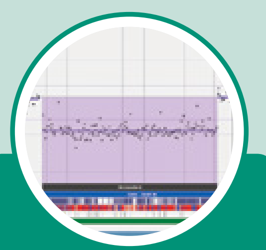


Step 4 Scanning

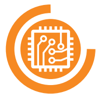
Slides are scanned — each spot shows the relative amounts of sample vs reference DNA at a particular genomic sequence



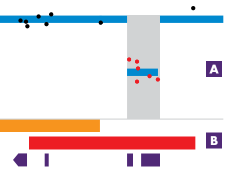
Once scanned, each spot indicates the relative amounts of the sample DNA against the reference DNA at the respective genomic locus. Spots with less sample than reference are indicative of a loss, those with more sample than reference are indicative of a gain



Step 5 Analysis



Purpose-built software allows for analysis and interpretation of aCGH results



A Probe and variant visualisation

B Database tracks

CytoSure Interpret software uses sophisticated algorithms to define areas of CNV or LOH. Track-based analysis allows for interpretation of these regions against external and internal databases

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Troubleshooting for arrays

Wet-lab processing is key to achieving the highest quality array data. This quick reference provides an overview of common problems and solutions to improve your data quality. Additional troubleshooting guidelines can be found on www.ogt.com/arrays.

Important QC metrics

DLRS values

This is perhaps the most important QC metric and calculates the probe-to-probe log ratio noise of an array. A poor Derivative Log Ratio Spread (DLRS) will mean that it is more difficult to accurately call amplifications or deletions. The DLRS value should be <0.3. Higher values can indicate poor quality DNA. To detect very small aberrations, a DLRS value of <0.2 may be required. An excellent array would have a DLRS value of around 0.15; although for some sample types (e.g., formalin fixed paraffin embedded), this may be difficult to achieve. Check the quality of the DNA on a high percentage agarose gel for degradation. If the DNA is degraded, shown by a smear on the gel, re-extract the sample.

Signal to Noise

This value is calculated by dividing the signal intensity by the background noise and indicates how clearly the spots can be detected above the background level. This metric is dependent on how well the sample labelling and washing steps worked. It is often easier to look at this metric first and then, if it does not pass, identify where the problem occurred by looking at the background noise and the signal intensity. An excellent value for signal to noise would be above 100, between 100 and 30 is good but below 30 is poor. It is difficult to reliably detect aberrations on arrays where the Signal-to-Noise is <30.

Background Noise

This metric is calculated as the standard deviation of negative control probes on the array. The values are recorded for both the green and red channel and can be classified into Excellent, Good and Poor. The values will depend on the array format being used. A poor background does not necessarily indicate that the array has failed. This is a secondary metric as it is incorporated into the Signal-to-Noise metric.

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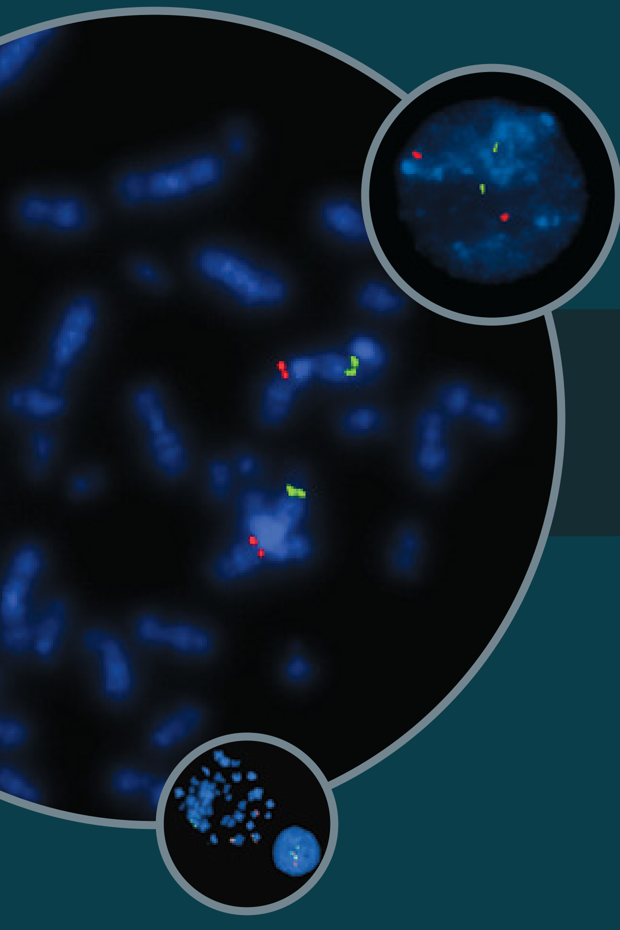
PROBLEM	IDENTIFIER	SOLUTION
Low A260/280 values	Protein Contamination	Re-purify samples using proteinase steps
High A260/280 values	RNA Contamination	Ensure that your DNA extraction protocol includes RNase
Low A260/230 values	Contamination of salts or solvents (e.g. Phenol)	Re-purified by ethanol precipitation Resuspending the DNA in TE buffer
Inaccurate Sample Concentration	High DNA concentration (>350ng/µl)	Dilute DNA 1:2 in water or suitable buffer
Low Dye Incorporation– (poor pmol/µl or DNA concentration values)	The wrong temperatures or times are being used	Check temperatures with a calibrated thermometer Check incubation times against protocol
	Incorrect volumes used in mastermix preparation	Check correct volumes are being added Check pipettes are calibrated correctly
	Insufficient mixing of samples, reagents and mastermixes	Gently vortex all reagent tubes (except Klenow) Flick mix Klenow tube Briefly spin to drive contents off tube walls
	Too much exposure to light or air	Use a closed thermal cycler with heated lid
	Loss of solution from evaporation	Use PCR machine with a heated lid If using tubes, make sure lids are tightly closed If using plates, use caps not a plate sealer
Black holes on array	Low volume of Hybridisation solution	Ensure the correct volume of hybridisation solution has been used Check no leakage of hybridisation solution has occurred
Non-uniform signal intensities	Split, deformity or crack in backing slide	Check the backing slide seal is intact and has not cracked Report any gasket slide failures to support@ogt.com
Bubble Scarring/Scotching	Jig assembly untouched for too long after hybridisation oven rotation malfunction	Check oven rotators are working Remove jigs from oven one at a time Disassemble under wash buffer rapidly
Fluorescent smears across the slide	Wash-step contamination with fluorescent material Dried-out arrays during the hybridisation or wash steps	Ensure dishes are regularly cleaned with appropriate solvent Ensure clean gloves, forceps and dishes Carry out additional acetonitrile wash for 1min at room temp
High Background Signal	Wash-step contamination with fluorescent material Wash conditions not stringent enough	Ensure dishes are regularly cleaned with appropriate solvent Ensure clean gloves and forceps Check stirrer is producing a vortex prior to adding slides in wash buffer Check temperature of oven and washes
Poor Signal intensity	Overly stringent wash or hybridisation conditions Cy5-labelled DNA was exposed to light	Check protocol for correct wash instructions Cover tubes with foil or use amber tubes Check temperature of oven and washes
Low Cy5 signal towards the edges of a feature	Wet ozone: outer edges of features dry quicker than inside, exposing edges to ozone	Ensure slides are scanned immediately after washing Enclose scanners in a box with ozone scrubbers
Low Cy5 signal gradient with more signal loss at one end of the slide	Dry ozone: Degradation during scanning, with exposed end degrading quicker	



Indices of FISH probes

Aquarius® Haematology Probe Range Summary

Probe Name	Chromosome Region	Probe Type	Control probe	No. Tests	Cat. No.*	Page
13q14.3	13q14.2-q14.3	Deletion	D13S1825	5 or 10	LPH 006	25
Alpha Satellite 12 *Plus* for CLL	12p11.1-q11.1	Enumeration	–	5 or 10	LPH 069	12
AML1 (RUNX1)	21q22.1	Breakapart	–	5 or 10	LPH 027	13
AML1/ETO (RUNX1/ RUNX1T1) Dual Fusion	21q22.1/8q21.3	Translocation	–	5 or 10	LPH 026	14
ATM	11q22.3	Deletion	D11Z1	5 or 10	LPH 011	15
BCL6	3q27.3	Breakapart	–	5 or 10	LPH 035	16
BCR/ABL (ABL1) Dual Fusion	22q11.22-q11.23/9q34.11-q34.12	Translocation	–	5 or 10	LPH 007	17
BCR/ABL (ABL1) *Plus* Dual Fusion	22q11.22-q11.23/9q34.11-q34.12	Translocation	–	5 or 10	LPH 038	18
CBFβ (CBFB)/MYH11 Dual Fusion	16p13.1/16q22	Translocation	–	5 or 10	LPH 022	19
CKS1B/CDKN2C (P18)	1p32.3/1q21.3	Amplification/ Deletion	–	5 or 10	LPH 039	20
cMYC (MYC)	8q24.21	Breakapart	–	5 or 10	LPH 010	23
CRLF2	Xp22.33/Yp11.32	Breakapart	–	50µl or 100µl	RU-LPH 085**	24
D13S319/13qter/12cen	13q14.2-q14.3/12p11.1-q11.1	Deletion/ Enumeration	LAMP1	5 or 10	LPH 066	27
D13S319 *Plus*	13q14.2-q14.3	Deletion	LAMP1	5 or 10	LPH 068	25
D13S25	13q14.3	Deletion	D13S1825	5 or 10	LPH 043	25
Del(5q)	5p15.31/5q31.2	Deletion	5p15.3	5 or 10	LPH 024	28
Del(7q)	7q22/7q31.2	Deletion	–	5 or 10	LPH 025	29
Del(20q)	20q12/20q13.1	Deletion	–	5 or 10	LPH 020	30
E2A (TCF3)	19p13.3	Breakapart	–	5 or 10	LPH 019	31
E2A (TCF3)/PBX1 Dual Fusion	19p13.3/1q23.3	Translocation	–	5 or 10	LPH 079	32
E2A (TCF3)/PBX1 *Plus* Translocation	19p13.3/1q23.3/17q22	Translocation	–	5 or 10	LPH 080	33
EVI1 (MECOM)	3q26.2	Breakapart	–	5 or 10	LPH 036	34
FIP1L1/CHIC2/PDGFRA	4q12	Deletion/Fusion	–	5 or 10	LPH 032	35
IGH	14q32.3	Breakapart	–	5 or 10	LPH 014	36
IGH *Plus*	14q32.3	Breakapart	–	5 or 10	LPH 070	37
IGH/BCL2 *Plus* Dual Fusion	14q32.3/18q21.33	Translocation	–	5 or 10	LPH 071	38
IGH/CCND1 *Plus* Dual Fusion	14q32.3/11q13.3	Translocation	–	5 or 10	LPH 072	39
IGH/CCND3 *Plus* Dual Fusion	14q32.3/6p21	Translocation	–	5 or 10	LPH 075	40
IGH/cMYC (MYC) *Plus* Dual Fusion	14q32.3/8q24.21	Translocation	–	5 or 10	LPH 076	41
IGH/FGFR3 *Plus* Dual Fusion	14q32.3/4p16.3	Translocation	–	5 or 10	LPH 074	42
IGH/MAF *Plus* v2 Dual Fusion	14q32.3/16q23	Translocation	–	5 or 10	LPH 108	43
IGH/MAFB *Plus* Dual Fusion	14q32.3/20q12	Translocation	–	5 or 10	LPH 077	44
IGH/MYEOV *Plus* Dual Fusion	14q32.3/11q13.3	Translocation	–	5 or 10	LPH 078	45
IGK	2p11.2	Breakapart	–	5 or 10	LPH 034	46
IGL	22q11.21-q11.23	Breakapart	–	5 or 10	LPH 033	46
MLL (KMT2A)	11q23.3	Breakapart	–	5 or 10	LPH 013	47
MLL (KMT2A)/AFF1 Dual Fusion	11q23.3/4q21.3-q22.1	Translocation	–	5 or 10	LPH 081	48
MLL (KMT2A)/MLLT1 Translocation	11q23.3/19p13.3	Translocation	–	50µl or 100µl	RU-LPH 082**	49

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S
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Aquarius® Haematology Probe Range Summary

Probe Name	Chromosome Region	Probe Type	Control probe	No. Tests	Cat. No.*	Page
MLL (KMT2A)/MLLT3 Translocation	11q23.3/9p21.3	Translocation	–	50µl or 100µl	RU-LPH 083**	50
MLL (KMT2A)/MLLT4 (AFDN) Translocation	11q23.3/6q27	Translocation	–	50µl or 100µl	RU-LPH 084**	50
MYB	6q23.3	Deletion	D6Z1 6p11.1-q11.1	5 or 10	LPH 016	51
P16 (CDKN2A)	9p21.3	Deletion	D9Z3 9q12	5 or 10	LPH 009	52
P2RY8	Xp22.33/Yp11.32	Deletion	–	50µl or 100µl	RU-LPH 086**	24
P53 (TP53)	17p13/11q22.3	Deletion	D17Z1 17p11.1-q11.1	5 or 10	LPH 017	53
P53 (TP53)/ATM Probe Combination	17p13/11q22.3	Deletion	–	5 or 10	LPH 052	54
PDGFRB	5q32	Breakapart	–	5 or 10	LPH 031	55
FAST PML/RARα (RARA) Dual Fusion	15q24.1/17q21.1-q21.2	Translocation	–	5 or 10	LPH 064	56
PML/RARα (RARA) Dual Fusion	15q24.1/17q21.1-q21.2	Translocation	–	5 or 10	LPH 023	57
RARα (RARA)	17q21.1-q21.2	Breakapart	–	5 or 10	LPH 065	58
TCL1	14q32.13/14q32.2	Breakapart	–	5 or 10	LPH 046	59
TCRAD	14q11.2	Breakapart	–	5 or 10	LPH 047	60
TCRB (TRB)	7q34	Breakapart	–	5 or 10	LPH 048	61
TEL/AML1 (ETV6/RUNX1) Dual Fusion	12p13.2/21q22.1	Translocation	–	5 or 10	LPH 012	62
TLX1	10q24.31	Breakapart	–	5 or 10	LPH 049	63
TLX3	5q35.1	Breakapart	–	5 or 10	LPH 050	64

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S
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CLL PROFILER Kit, LPH 067*

Product Description	Chromosome Region	Probe Type	Control Probe	No. Tests	Page
P53 (TP53)/ATM	17p13.1/11q22.3	Deletion	–	5 or 10	21
D13S319/13qter/12cen	13q14.2-14.3/12p11.1-q11.1	Deletion/Enumeration	LAMP1	5 or 10	21

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S

CLL *Plus* Screening Panel, LPH 087*

Product Description	Chromosome Region	Probe Type	Control Probe	No. Tests	Page
P53 (TP53)	17p13	Deletion	D17Z1	5 or 10	22
ATM	11q22.3	Deletion	D11Z1	5 or 10	22
MYB	6q23	Deletion	D6Z1	5 or 10	22
13q14.3	13q14.3	Deletion	D13S1825	5 or 10	22
Alpha Satellite 12 *Plus* for CLL	12p11.1-q11.1	Enumeration	–	5 or 10	22

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S

Chromoprobe Multiprobe® - ALL v2 System Range Summary

Product Description	No. of Devices	Cat. No.	Page
Chromoprobe Multiprobe® - ALL v2	2	PMP 030	68
Chromoprobe Multiprobe® - ALL v2	5	PMP 031	68
Chromoprobe Multiprobe® - ALL v2	10	PMP 032	68
Chromoprobe Multiprobe® - ALL v2	20	PMP 033*	68

* Supplied as 4 x 5 Multiprobe devices

Chromoprobe Multiprobe® - CLL System Range Summary

Product Description	No. of Devices	Cat. No.	Page
Chromoprobe Multiprobe® - CLL	2	PMP 018	70
Chromoprobe Multiprobe® - CLL	5	PMP 017	70
Chromoprobe Multiprobe® - CLL	10	PMP 016	70
Chromoprobe Multiprobe® - CLL	20	PMP 020*	70

* Supplied as 4 x 5 Multiprobe devices

Chromoprobe Multiprobe® - AML/MDS System Range Summary

Product Description	No. of Devices	Cat. No.	Page
Chromoprobe Multiprobe® - AML/MDS	2	PMP 025	72
Chromoprobe Multiprobe® - AML/MDS	5	PMP 026	72
Chromoprobe Multiprobe® - AML/MDS	10	PMP 027	72
Chromoprobe Multiprobe® - AML/MDS	20	PMP 028*	72

* Supplied as 4 x 5 Multiprobe devices

Aquarius® Tissue Pretreatment Kit Summary

Product Description	Kit Format	Cat. No.	Page
Aquarius Tissue Pretreatment Kit*	Reagent 1 (1x1L), Reagent 2 (1x10ml)	LPS 100	93

* This product is provided under an agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostic or life science use only.

Aquarius® Haematopathology Probe Range Summary

Probe Name	Chromosome Region	Probe Type	Control Probe	No. Tests	Cat. No.*	Page
BCL2 Breakapart	18q21.33-q22.1	Breakapart	–	5 or 10	LPS 028	77
BCL6 Breakapart	3q27.3-q28	Breakapart	–	5 or 10	LPS 029	78
CCND1 Breakapart	11q13.3	Breakapart	–	5 or 10	LPS 030	79
IGH Breakapart	14q32.3	Breakapart	–	5 or 10	LPS 032	80
IGH/BCL2 Translocation, Dual Fusion	14q32.3/18q21.33	Translocation	–	5 or 10	LPS 033	81
IGH/CCND1 Translocation, Dual Fusion	14q32.3/11q13.3	Translocation	–	5 or 10	LPS 031	82
IGH/MALT1 Translocation, Dual Fusion	14q32.3/18q21.31-q21.32	Translocation	–	5 or 10	LPS 034	83
IGH/MYC Translocation, Dual Fusion	14q32.3/8q24.21	Translocation	–	5 or 10	LPS 035	84
IGK Breakapart	2p11.2	Breakapart	–	5 or 10	LPS 038	85
IGL Breakapart	22q11.21-q11.23	Breakapart	–	5 or 10	LPS 039	85
MALT1 Breakapart	18q21.31-q21.32	Breakapart	–	5 or 10	LPS 017	86
MYC Breakapart	8q24.21	Breakapart	–	5 or 10	LPS 027	87
P16 (CDKN2A) Deletion	9p21.3	Deletion	D9Z3	5 or 10	LPS 036	88
P53 (TP53) Deletion	17p13	Deletion	D17Z1	5 or 10	LPS 037	89
RB1 Deletion	13q14.2	Deletion	LAMP1	5 or 10	LPS 011	90

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S

Aquarius® Pathology Probe Range Summary

Probe Name	Chromosome Region	Probe Type	Control Probe	No. Tests	Cat No.*	Page
Tissue Pretreatment Kit					LPS 100	93
1p36/1q25 and 19q13/19p13 Deletion Probe Kit	1p36.32/19q13.33	Deletion	1q25/19p13	5 or 10	LPS 047	94
ALK Breakapart	2p23.2-p23.1	Breakapart	–	5 or 10	LPS 019	95
CHOP (DDIT3) Breakapart	12q13.3	Breakapart	–	5 or 10	LPS 015	96
C-MET (MET) Amplification	7q31.2	Amplification	D7Z1	5 or 10	LPS 004	97
EGFR Amplification	7p11.2	Amplification	D7Z1	5 or 10	LPS 003	98
EML4 Breakapart	2p21	Breakapart	–	5 or 10	LPS 020	99
EWSR1 Breakapart	22q12.1-q12.2	Breakapart	–	5 or 10	LPS 006	100
EWSR1/ERG Translocation, Dual Fusion	22q12.1-q12.2/21q22.13-q22.2	Translocation	–	5 or 10	LPS 008	101
FLI1/EWSR1 Translocation, Dual Fusion	11q24.3/22q12.1-q12.2	Translocation	–	5 or 10	LPS 007	102
FGFR1 Breakapart/Amplification	8p11.23-p11.22	Breakapart/ Amplification	D8Z2	5 or 10	LPS 018	103
FOXO1 Breakapart	13q14.1	Breakapart	–	5 or 10	LPS 049	104
FUS Breakapart Probe	16p11.2	Breakapart	–	5 or 10	LPS 050	105
HER2 (ERBB2) Amplification	17q12	Amplification	D17Z1	5 or 10	LPS 001	106
MDM2 Amplification	12q15	Amplification	D12Z1	5 or 10	LPS 016	107
N-MYC (MYCN) Amplification	2p24.3/2q11.2	Amplification	AFF3	5 or 10	LPS 009	108

Aquarius® Pathology Probe Range Summary

Probe Name	Chromosome Region	Probe Type	Control Probe	No. Tests	Cat No.*	Page
PAX3 Breakapart	2q36.1	Breakapart	–	5 or 10	LPS 012	109
PAX7 Breakapart	1p36.13	Breakapart	–	5 or 10	LPS 013	109
RET Breakapart	10q11.21	Breakapart	–	5 or 10	LPS 045	111
ROS1 Breakapart	6q22.1	Breakapart	–	5 or 10	LPS 022	112
ROS1 *Plus* Breakapart	6q22.1	Breakapart	–	5 or 10	LPS 046	113
SRD (CHD5) Deletion	1p36.31	Deletion	ZNF672	5 or 10	LPS 010	114
SYT (SS18) Breakapart	18q11.2	Breakapart	–	5 or 10	LPS 014	115
TFE3 Breakapart [RUO]**	Xp11.23	Breakapart	–	50ul /100ul	RU-LPS 051**	116
TMPRSS2/ERG Deletion/Breakapart	21q22.2-q22.3/21q22.13-q22.2	Deletion/ Breakapart	ERG	5 or 10	LPS 021	117
TOP2A Amplification/Deletion	17q21.2	Amplification/ Deletion	D17Z1	5 or 10	LPS 002	118
ZNF217 Amplification	20q13.2	Amplification	DEFB128	5 or 10	LPS 005	119

* For 5 test kit add -S to catalogue number, e.g: LPH ###-S
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Aquarius® *FAST* FISH Prenatal Probe Range Summary

Product Description	Locus	Chromosome Region	No. Tests	Cat. No.*	Page
Probe Set 1 and 2			5, 10, 30 or 50	LPF 001	123
X centromere	DXZ1	Xp11.1-q11.1			
Y centromere	DYZ3	Yp11.1-q11.1			
18 centromere	D18Z1	18p11.1-q11.1			
13 unique sequence	N/A	13q14.2			
21 unique sequence	N/A	21q22.13			
Probe Set 1			5 or 10	LPF 002	123
X centromere	DXZ1	Xp11.1-q11.1			
Y centromere	DYZ3	Yp11.1-q11.1			
18 centromere	D18Z1	18p11.1-q11.1			
Probe Set 2			5 or 10	LPF 003	123
13 unique sequence	N/A	13q14.2			
21 unique sequence	N/A	21q22.13			

* For 5, 30 or 50 test kit add -S, -30 or -50 to the catalogue number respectively, e.g: LPF### -S, LPF### -30 or LPF### -50

Aquarius® Prenatal Probe Range Summary

Product Description	Locus	Chromosome Region	No. Tests	Cat. No.*	Page
Probe Set 1 and 2			5, 10, 30 or 50	LPA 001	124
X centromere	DXZ1	Xp11.1-q11.1			
Y centromere	DYZ3	Yp11.1-q11.1			
18 centromere	D18Z1	18p11.1-q11.1			
13 unique sequence	N/A	13q14.2			
21 unique sequence	N/A	21q22.13			
Probe Set 1			5 or 10	LPA 002	124
X centromere	DXZ1	Xp11.1-q11.1			
Y centromere	DYZ3	Yp11.1-q11.1			
18 centromere	D18Z1	18p11.1-q11.1			
Probe Set 2			5 or 10	LPA 003	124
13 unique sequence	N/A	13q14.2			
21 unique sequence	N/A	21q22.13			
Probe Set 3			5 or 10	LPA 005	124
13 unique sequence	N/A	13q14.2			
18 centromere	D18Z1	18p11.1-q11.1			
21 unique sequence	N/A	21q22.13			
18 centromere blue	D18Z1	18p11.1-q11.1	5 or 10	LPA 004	124

* For 5, 30 or 50 test kit add -S, -30 or -50 to the catalogue number respectively, e.g: LPF### -S, LPF### -30 or LPF### -50

Aquarius® Microdeletion Probe Range Summary

Probe name	Chromosome Region	Probe Loci	Control Probe	No. Tests	Cat. no.*	Page
Angelman (UBE3A/D15S10)	15q11.2-q12	UBE3A/D15S10	15qter	5 or 10	LPU 006	127
Cri-Du-Chat and Sotos Probe Combination	5p15.31/5p15.2/5q35	UBE2QL1, CTNND2, NSD1	–	5 or 10	LPU 013	128
DiGeorge II (10p14)	10p14	CELF2	D10Z1	5 or 10	LPU 015	129
DiGeorge/VCFS TUPLE1 and 22q13.3 Deletion Syndrom Probe Combination	22q11.2/ 22q13.3	TUPLE1, SHANK3	–	5 or 10	LPU 004	131
DiGeorge/VCFS N25 and 22q13.3 Deletion Syndrome Probe Combination	22q11.21/22q13.3	N25/D22S75, SHANK3	–	5 or 10	LPU 010	131
DiGeorge TBX1 Region and 22q13.3 Region	22q11.21/22q13.3	TBX1, SHANK3	–	5 or 10	LPU 014	131
Kallmann (KAL1) and Steroid Sulphatase Deficiency (STS) Probe Combination	Xp22.31	KAL1 (ANOS1), STS	DXZ1	5 or 10	LPU 016	132
Prader-Willi/Angelman (SNRPN)	15q11.2	SNRPN	15qter	5 or 10	LPU 005	133
Saethre-Chotzen (Region)/Williams-Beuren (Region Probe) Combination	7p21.1/7q11.23	TWIST1, WBSCR/ELN	–	5 or 10	LPU 024	134
SHOX	Xp22.33/Yp11.32	SHOX	DXZ1, DYZ1	5 or 10	LPU 025	135
Smith-Magenis (RAI1)/Miller-Dieker Probe Combination	17p11.2/17p13.3	RAI1, PAFAH1B1	–	5 or 10	LPU 019	136
SRY	Yp11.31	SRY	DXZ1, DYZ1	5 or 10	LPU 026	137
Williams-Beuren	7q11.23	WBSCR/ELN	D7Z1	5 or 10	LPU 011	138
Wolf-Hirschhorn	4p16.3	MMSET, NEFLA	4qter	5 or 10	LPU 009	139

* For 5 test kit add -S to catalogue number, e.g: LPU ###-S

Aquarius® Satellite Enumeration Probe Range Summary

Chromosome	Locus	Chromosome Region	DNA Class	No. Tests	Cat. No.*	Page
1	D1Z1	1q12	satellite III	5	LPE 001R/G	143
2	D2Z2	2p11.1-q11.1	α-satellite	5	LPE 002R/G	143
3	D3Z1	3p11.1-q11.1	α-satellite	5	LPE 003R/G	143
4	D4Z1	4p11.1-q11.1	α-satellite	5	LPE 004R/G	143
1/5/19	D1Z7	1p11.1-q11.1	α-satellite	5	LPE 005R/G	143
	D5Z2	5p11.1-q11.1				143
	D19Z3	19p11.1-q11.1				143
6	D6Z1	6p11.1-q11.1	α-satellite	5	LPE 006R/G	143
7	D7Z1	7p11.1-q11.1	α-satellite	5	LPE 007R/G	143
8	D8Z2	8p11.1-q11.1	α-satellite	5	LPE 008R/G	143
	D8Z2	8p11.1-q11.1	α-satellite	10	LPE 008B	144
9	D9Z3	9q12	satellite III	5	LPE 009R/G	143
10	D10Z1	10p11.1-q11.1	α-satellite	5	LPE 010R/G	143
11	D11Z1	11p11.1-q11.1	α-satellite	5	LPE 011R/G	143
12	D12Z3	12p11.1-q11.1	α-satellite	5	LPE 012R/G	143
	D12Z3	12p11.1-q11.1	α-satellite	10	LPE 012B	144
13/21	D13Z1	13p11.1-q11.1	α-satellite	5	LPE 013R/G	143
	D21Z1	21p11.1-q11.1				143
14/22	D14Z1	14p11.1-q11.1	α-satellite	5	LPE 014R/G	143
	D22Z1	22p11.1-q11.1				143
15	D15Z4	15p11.1-q11.1	α-satellite	5	LPE 015R/G	143
16	D16Z2	16p11.1-q11.1	α-satellite	5	LPE 016R/G	143
17	D17Z1	17p11.1-q11.1	α-satellite	5	LPE 017R/G	143
	D17Z1	17p11.1-q11.1	α-satellite	10	LPE 017B	144
18	D18Z1	18p11.1-q11.1	α-satellite	5	LPE 018R/G	143
20	D20Z1	20p11.1-q11.1	α-satellite	5	LPE 020R/G	143
X	DXZ1	Xp11.1-q11.1	α-satellite	5	LPE 0XR/G	143
Yc	DYZ3	Yp11.1-q11.1	α-satellite	5	LPE 0YcR/G	143
Yq	DYZ1	Yq12	satellite III	5	LPE 0YqR/G	143
XYc Dual Labeled	DXZ1	Xp11.1-q11.1	α-satellite	10	LPE 0XYc	144
	DYZ3	Yp11.1-q11.1				
XYq Dual Labeled	DXZ1	Xp11.1-q11.1	α-satellite	10	LPE 0XYq	144
	DYZ1	Yq12	satellite III			

* R specifies a red label and G specifies a green label and B specifies a blue label.

Acro-P-Arm Probe

Chromosome	Color	No. Tests	Cat. No.	Page
13, 14, 15, 21, 22	Red	10	LPE NOR	145

Aquarius® Subtelomere Specific Probe Range Summary

Probe Specificity	Clone Name	Marker (STS)	Max. physical distance from Telomere (kb)	Cat. No.*	Page
1p	CEB108	RH120573	987	LPT 01PR/G	149
1q	160H23	GDB:315525	54	LPT 01QR/G	149
2p	dJ892G20	D2S2983	18	LPT 02PR/G	149
2q	dJ1011O17	D2S2986	277	LPT 02QR/G	149
2q NP	172I13	D2S447	311	LPT 02QNPR/G	149
3p	dJ1186B18	D3S4559	213	LPT 03PR/G	149
3q	196F4	D3S1272	959	LPT 03QR/G	149
4p	36P21	D4S3360	67	LPT 04PR/G	149
4q	dJ963K6	D4S139	372	LPT 04QR/G	149
5p	189N21	RH120167	2254	LPT 05PR/G	149
5q	240G13	D5S2907	222	LPT 05QR/G	149
6p	62I11	STS-H99640	147	LPT 06PR/G	149
6q	57H24	D6S2522	230	LPT 06QR/G	149
7p	109a6	RH104000	118	LPT 07PR/G	149
7q	2000a5	RH48601	138	LPT 07QR/G	149
8p	dJ580L5	RH40619	150	LPT 08PR/G	149
8q	489D14	D8S595	202	LPT 08QR/G	149
9p	43N6	RH65569	226	LPT 09PR/G	149
9q	112N13	D9S2168	167	LPT 09QR/G	149
10p	306F7	STS-N35887	271	LPT 10PR/G	149
10q	137E24	RH44494	138	LPT 10QR/G	149
11p	dJ908H22	D11S2071	189	LPT 11PR/G	149
11q	dJ770G7	D11S4974	3447	LPT 11QR/G	149
12p	496A11	D12S200	771	LPT 12PR/G	149
12q	221K18	RH81094	90	LPT 12QR/G	149
13q	163C9	D13S1825	17	LPT 13QR/G	149
14q	dJ820M16	D14S1420	143	LPT 14QR/G	149
15q	154P1	D15S936	328	LPT 15QR/G	149
16p	121I4	SHGC-16929	147	LPT 16PR/G	149
16q	240G10	RH80305	331	LPT 16QR/G	149
17p	2111b1	D17S2199	143	LPT 17PR/G	149
17q	362K4	–	34	LPT 17QR/G	149
18p	74G18	D18S552	141	LPT 18PR/G	149
18q	dJ964M9	D18S1390	155	LPT 18QR/G	149
19p	dJ546C11	D19S676E	260	LPT 19PR/G	149
19q	F21283	RH102404	49	LPT 19QR/G	149
20p	dj1061L1	D20S210	165	LPT 20PR/G	149
20q	81F12	RH10656	153	LPT 20QR/G	149
21q	63H24	D21S1446	29	LPT 21QR/G	149
22q	99K24	D22S1726	101	LPT 22QR/G	149
XpYp**	839D20	DXYS129	344	LPT XYPR/G	149
XqYq***	225F6 C8.2/1	DXYS154 SYBL1	64 131	LPT XYQR/G LPT XYQR/G	149

* R specifies a red label, G specifies a green label
** This probe is specific for the p-arms of both X and Y
*** This probe is specific for the q-arms of both X and Y
NP Non Polymorphic

Telomark

Probe Specificity	Marker (STS)	Max. physical distance from Telomere (kb)	Notes and Source	Cat. No.*	Page
1p	SHGC-74122	848	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK01	150
1q	GDB:315525	54	TelomereA6 / CTB-160H23 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK01	150
2p	D2S2983	18	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK02	150
2q NP	D2S447	311	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK02	150
3p	D3S4559	213	TelomereA3 / PAC1186B18 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK03	150
3q	RH12742	388	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK03	150
4p	D4S3360	67	TelomereA5 / CTC-36P21 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK04	150
4q	D4S139	371	Sequenced - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK04	150
5p	D5S1680E	372	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK05	150
5q	D5S2907	222	TelomereA7 / CTC-240G13 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK05	150
6p	STS-H99640	147	TelomereA8 / CTB-62I11 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK06	150
6q	D6S2522	230	TelomereA9 / CTB-57H24 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK06	150
7p	RH104000	118	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK07	150
7q	RH48601	138	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK07	150
8p	D8S1482	407	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK08	150
8q	D8S595	202	TelomereA12 / CTC-489D14 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK08	150
9p	RH65569	226	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK09	150
9q	D9S1090	385	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK09	150
10p	STS-N35887	271	TelomereB1 / CTC-306F7 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK10	150
10q	RH102433	108	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK10	150
11p	D11S2071	189	TelomereB3 / CTC-908H22 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK11	150
11q	D11S1110	764	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK11	150
12p	D12S200	771	TelomereB5 / CTC-496A11 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK12	150
12q	RH81094	90	TelomereB6 / CTC-221K18 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK12	150
13q	D13S1825	17	Sequenced - UCSC hg38 (2013)	LPT MRK/LPT MRK06	150
14q	D14S1420	143	TelomereB8 / CTC-820M16 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK07	150
15q	D15S936	328	TelomereB9 / CTB-154P1 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK10	150
16p	SHGC-16929(UCSC)	147	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK13	150
16q	RH80305	331	TelomereB11 / CTC-240G10 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK13	150
17p	D17S2199	143	Sequenced - UCSC hg38 (2013)	LPT MRK/LPT MRK08	150
17q	SHGC-144868	399	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK09	150
18p	D18S552	141	TelomereG9 / GS1-74G18 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK11	150
18q	D18S1390	155	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK12	150
19p	D19S676E	260	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK14	150
19q	RH102404	49	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK14	150
19q	D19S829	178	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK14	150
20p	D20S210	165	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK15	150
20q	RH10656	153	Sequenced - UCSC hg38 (2013)	LPT MRK/LPT MRK15	150
21q	D21S1446	29	TelomereC3 / CTB-63H24 - Ensembl Ver.75 (2014)	LPT MRK/LPT MRK04	150
22q	D22S1726	101	Sequenced - Ensembl Ver.55 (2009)	LPT MRK/LPT MRK03	150
XpYp	DXYS129	288	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK01	150
XpYp	DXYS129	331	Ensembl Ver.74 (GRCh37) 2013	LPT MRK/LPT MRK01	150
XqYq	DXYS154	64	Flanking PCR est. - Ensembl Ver.74 (2013)	LPT MRK/LPT MRK02	150

Accessories

Cat. No.	Description	Unit Size
PCN009	Porcelain Wash Jars - 12 Slide Capacity	2
PCN004	Hybridisation Chamber	1
PCN007	24 Square Template Slides	100
PCN008	8 Square Template Slides	100
PCN002	Slide Surface Thermometer	4

Ancillary Reagents

Cat. No.	Description	Unit Size
DES500L	0.125µg/ml DAPI	500µl
DES1000L	0.125µg/ml DAPI	1000µl
DFS500L	1.0µg/ml DAPI	500µl
DSS500L	0.0625µg/ml DAPI	500µl
HB500L	Hybridisation Solution B	500µl
HB1000L	Hybridisation Solution B	1000µl
LPS100	Aquarius® Tissue Pretreatment Kit*	Reagent 1 (1x1L) Reagent 2 (1x10ml)
PCA003	20x SSC	100ml
PCA005	Rubber Solution Glue	15g
PCN003	Mounting Medium	10ml

Microscope Filters**

Cat. No.	Description	Unit Size
CF69008	Chroma® Filter: 69008 ET-Aqua/FITC/Texas Red Triple Filter Set	1
CF69011	Chroma® Filter: 69011 ET-Aqua/Green/Orange Triple Filter Set	1
CF49000	Chroma® Filter: 49000 ET-DAPI Single Filter	1
CF49302	Chroma® Filter: 49302 ET-Aqua Single Filter	1
CF49303	Chroma® Filter: 49303 ET-Green Single Filter	1
CF49306	Chroma® Filter: 49306 ET-Red Single Filter	1
CF59010	Chroma® Filter: 59010 ET-Green/Red Dual Filter	1
CF59011	Chroma® Filter: 59011 ET-Green/Orange Dual Filter	1
CF59022	Chroma® Filter: 59022 ET-FITC/Texas Red Dual Filter	1

Blocks

Cat. No.	Description	Unit Size
CBZ0001	Chroma® Block: Zeiss Microscope	1
CBBX051	Chroma® Block: Olympus BX51	1
CBBX061	Chroma® Block: Olympus BX61	1
CBNK050	Chroma® Block: Nikon 50i	1
CBDM550	Chroma® Block: Leica DM5500	1

* LPS100 is provided under agreement between Life Technologies Corporation and Cytocell Ltd and is available for human diagnostics or life science use only.
** Microscope filters are available on request. These filters can be ordered with or without a filter cube.
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Index by Chromosome

Chromosome Region	Product Name	Control Region	Cat. No.	Page
1-22, X, Y	Aquarius® Satellite Enumeration Probes	–	LPE xxxR/G	143
1-22, X, Y	Aquarius® Subtelomere Specific Probes	–	LPT xxxP/Q, R/G	149
1-22 X, Y	Aquarius TeloMark Kit	–	LPT MRK/ LPT MRKxx 161	150
1p36.31	SRD (CHD5) Deletion	1qter (1q44)	LPS 010	114
1p36.13	PAX7 Breakapart	–	LPS 013	109
1p36.32	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	1q25/19p13	LPS 047	94
1p32.3/1q21.3	CKS1B/CDKN2C (P18) Amplification/Deletion	–	LPH 039	20
1q21.3/1p32.3	CKS1B/CDKN2C (P18) Amplification/Deletion	–	LPH 039	20
1q23.3/19p13.3	E2A (TCF3)/PBX1 Translocation, Dual Fusion	–	LPH 079	32
1q23.3/17q22/19p13.3	E2A (TCF3)/PBX1 *Plus* Translocation, Dual Fusion	–	LPH 080	32
1q25.2	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	1q25/19p13	LPS 047	94
2p24.3/2q11.2	N-MYC (MYCN) Amplification	2q11	LPS 009	108
2p23.2-p23.1	ALK Breakapart	–	LPS 019	95
2p21	EML4 Breakapart	–	LPS 020	99
2p11.2	IGK Breakapart	–	LPH 034	46
2p11.2	IGK Breakapart (Haematopathology)	–	LPS 038	85
2q36.1	PAX3 Breakapart	–	LPS 012	109
3q26.2	EVI1 (MECOM) Breakapart	–	LPH 036	34
3q27.3	BCL6 Breakapart	–	LPH 035	16
3q27.3-q28	BCL6 Breakapart (Haematopathology)	–	LPS 029	78
4p16.3	Wolf-Hirschhorn	4qter	LPU 009	139
4p16.3/14q32.3	IGH/FGFR3 *Plus* Translocation, Dual Fusion	–	LPH 074	42
4q12	FIP1L1/CHIC2/PDGFRA Deletion/Fusion	–	LPH 032	35
4q21.3-q22.1/11q23.3	MLL (KMT2A)/AFF1 Translocation, Dual Fusion	–	LPH 081	48
5p15.31/5q31.2	Del(5q) Deletion	5p15.31	LPH 024	28
5p15.31/5p15.2/5q35	Cri-du-chat & Sotos Probe Combination	–	LPU 013	128
5p15.2/5p15.31/5q35	Cri-du-chat & Sotos Probe Combination	–	LPU 013	128
5q31.2/5p15.31	Del(5q) Deletion	5p15.31	LPH 024	28
5q32	PDGFRB Breakapart	–	LPH 031	55
5q35/5p15.31/5p15.2	Cri-du-chat & Sotos Probe Combination	–	LPU 013	128
5q35.1	TLX3 Breakapart	–	LPH 050	64
6p21/14q32.3	IGH/CCND3 *Plus* Translocation, Dual Fusion	–	LPH 075	40
6q22.1	ROS1 Breakapart	–	LPS 022	112
6q22.1	ROS1 *Plus* Breakapart	–	LPS 046	113
6q23.3	MYB Deletion	D6Z1	LPH 016	51
6q27/11q23.3	MLL (KMT2A)/MLLT4 (AFDN) Translocation, Dual Fusion	–	RU-LPH 084*	50
7p21.1/7q11.23	Saethre-Chotzen/Williams-Beuren Combination	–	LPU 024	134
7p11.2	EGFR Amplification	D7Z1	LPS 003	98
7q11.23	Williams-Beuren	D7Z1	LPU 011	138
7q11.23/7p21.1	Saethre-Chotzen/Williams-Beuren Combination	–	LPU 024	134
7q22.1-q22.2/7q31.2	Del(7q) Deletion	–	LPH 025	29

* For research use only, not for use in diagnostic procedures.

Index by Chromosome

Chromosome Region	Product Name	Control Region	Cat. No.	Page
7q31.2/7q22.1-q22.2	Del(7q) Deletion	–	LPH 025	29
7q31.2	C-MET (MET) Amplification	D7Z1	LPS 004	97
7q34	TCRB (TRB) Breakapart	–	LPH 048	61
8p11.23-p11.22	FGFR1 Breakapart/Amplification	D8Z2	LPS 018	103
8q21.3/21q22.12	AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion	–	LPH 026	14
8q24.21	cMYC (MYC) Breakapart	–	LPH 010	23
8q24.21	MYC Breakapart (Haematopathology)	–	LPS 027	87
8q24.21/14q32.3	IGH/cMYC(MYC) *Plus* Translocation, Dual Fusion	–	LPH 076	41
8q24.21/14q32.3	IGH/MYC Translocation, Dual Fusion (Haematopathology)	–	LPS 035	84
9p21.3/11q23.3	MLL (KMT2A)/MLLT3 Translocation, Dual Fusion	–	RU-LPH 083*	50
9p21.3	P16 (CDKN2A) Deletion	D9Z3	LPH 009	52
9p21.3	P16 (CDKN2A) Deletion (Haematopathology)	D9Z3	LPS 036	88
9q34.11-q34.12/22q11.22-q11.23	BCR/ABL (ABL1) Translocation, Dual Fusion	–	LPH 007	17
9q34.11-q34.12/22q11.22-q11.23	BCR/ABL (ABL1) Plus Translocation, Dual Fusion	–	LPH 038	18
10p14	DiGeorge II (10p14)	D10Z1	LPU 015	129
10q11.21	RET Breakapart	–	LPS 045	111
10q24.31	TLX1 Breakapart	–	LPH 049	63
11q13.3	CCND1 Breakapart (Haematopathology)	–	LPS 030	79
11q13.3/14q32.3	IGH/CCND1 *Plus* Translocation, Dual Fusion	–	LPH 072	39
11q13.3/14q32.3	IGH/CCND1 Translocation, Dual Fusion (Haematopathology)	–	LPS 031	82
11q13.3/14q32.3	IGH/MYEOV *Plus* Translocation, Dual Fusion	–	LPH 078	45
11q22.3	ATM Deletion	D11Z1	LPH 011	15
11q22.3/17p13.1	P53 (TP53)/ATM Probe Combination	–	LPH 052	54
11q23.3	MLL (KMT2A) Breakapart	–	LPH 013	47
11q23.3/4q21.3-q22.1	MLL (KMT2A)/AFF1 Translocation, Dual Fusion	–	LPH 081	48
11q23.3/6q27	MLL (KMT2A)/MLLT4 (AFDN)	–	RU-LPH 084*	50
11q23.3/9p21.3	MLL/MLLT3 Translocation, Dual Fusion	–	RU-LPH 083*	50
11q23.3/19p13.3	MLL/MLLT1 Translocation, Dual Fusion	–	RU-LPH 082*	49
11q24.3/22q12.1-q12.2	FLI1/EWSR1 Translocation, Dual Fusion	–	LPS 007	102
12p13.2/21q22.12	TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion	–	LPH 012	62
12p11.1-q11.1	Alpha Satellite 12 *Plus* for CLL	–	LPH 069	12
12q13.3	CHOP (DDIT3) Breakapart	–	LPS 015	96
12q15	MDM2 Amplification	D12Z1	LPS 016	107
13q14.1	FOXO1 Breakapart	–	LPS 049	104
13q14.2-q14.3	13q14.3 Deletion	13qter	LPH 006	25
13q14.2-14.3	D13S319 *Plus* Deletion	13qter	LPH 068	25
13q14.2/13q34/12cen	D13S319/13qter/12cen Deletion/Enumeration	13qter, D12Z3	LPH 066	27
13q14.2	RB1 Deletion	13qter	LPS 011	90
13q14.3	D13S25 Deletion	13qter	LPH 043	25
14q11.2	TCRAD Breakapart	–	LPH 047	60
14q32.13-q32.2	TCL1 Breakapart	–	LPH 046	59
14q32.3	IGH Breakapart	–	LPH 014	36

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14q32.3	IGH *Plus* Breakapart	–	LPH 070	37
14q32.3	IGH Breakapart (Haematopathology)	–	LPS 032	80
14q32.3/11q13.3	IGH/CCND1 *Plus* Translocation, Dual Fusion	–	LPH 072	39
14q32.3/11q13.3	IGH/CCND1 Translocation, Dual Fusion (Haematopathology)	–	LPS 031	82
14q32.3/11q13.3	IGH/MYEOV *Plus* Translocation, Dual Fusion	–	LPH 078	45
14q32.3/16q23	IGH/MAF *Plus* v2 Translocation, Dual Fusion	–	LPH 108	43
14q32.3/18q21.31-q21.32	IGH/MALT1 Translocation, Dual Fusion (Haematopathology)	–	LPS 034	83
14q32.3/18q21.33	IGH/BCL2 Plus Translocation, Dual Fusion	–	LPH 071	38
14q32.3/18q21.33-q22.1	IGH/BCL2 Translocation, Dual Fusion (Haematopathology)	–	LPS 033	81
14q32.3/20q12	IGH/MAFB *Plus* Translocation, Dual Fusion	–	LPH 077	44
14q32.3/4p16.3	IGH/FGFR3 *Plus* Translocation, Dual Fusion	–	LPH 074	42
14q32.3/6p21	IGH/CCND3 *Plus* Translocation, Dual Fusion	–	LPH 075	40
14q32.3/8q24.21	IGH/cMYC (MYC) *Plus* Translocation, Dual Fusion	–	LPH 076	41
14q32.3/8q24.21	IGH/MYC Translocation, Dual Fusion (Haematopathology)	–	LPS 035	84
15q11.2	Prader-Willi/Angelman (SNRPN)	15qter	LPU 005	133
15q11.2-q12	Angelman (UBE3A/D15S10)	15qter	LPU 006	127
15q24.1/17q21.1-q21.2	FAST PML/RARα (RARA) Translocation, Dual Fusion	–	LPH 064	56
15q24.1/17q21.1-q21.2	PML/RARα (RARA) Translocation, Dual Fusion	–	LPH 023	57
16p11.2	FUS Breakapart	–	LPS 050	105
16p13.1/16q22	CBFβ/MYH11 Translocation, Dual Fusion	–	LPH 022	19
16q22/16p13.1	CBFβ/MYH11 Translocation, Dual Fusion	–	LPH 022	19
16q23/14q32.3	IGH/MAF *Plus* v2 Translocation, Dual Fusion	–	LPH 108	43
17p13	P53 (TP53) Deletion	D17Z1	LPH 017	53
17p13	P53 (TP53) Deletion (Haematopathology)	D17Z1	LPS 037	89
17p13/11q22.3	P53 (TP53)/ATM Probe Combination	–	LPH 052	54
17p11.2/17p13.3	Smith-Magenis (RAI1)/Miller-Dieker Probe Combination	–	LPU 019	136
17q12	HER2 (ERBB2) Amplification	D17Z1	LPS 001	106
17q21.1-q21.2	RARα (RARA) Breakapart	–	LPH 065	58
17q21.1-q21.2/15q24.1	*FAST* PML/RARα (RARA) Translocation, Dual Fusion .	–	LPH 064	56
17q21.1-q21.2/15q24.1	PML/RARα (RARA) Translocation, Dual Fusion	–	LPH 023	57
17q21.2	TOP2A Amplification/Deletion	D17Z1	LPS 002	118
17q22/1q23.3/19p13.3	E2A (TCF3)/PBX1 Plus Translocation, Dual Fusion .	–	LPH 080	33
18q11.2	SYT (SS18) Breakapart	–	LPS 014	115
18q21.31-q21.32	MALT1 Breakapart	–	LPS 017	86
18q21.31-q21.32/14q32.3	IGH/MALT1 Translocation, Dual Fusion (Haematopathology)	–	LPS 034	83
18q21.33-q22.1	BCL2 Breakapart (Haematopathology)	–	LPS 028	77
18q21.33/14q32.3	IGH/BCL2 *Plus* Translocation, Dual Fusion	–	LPH 071	38
18q21.33-q22.1/14q32.3	IGH/BCL2 Translocation, Dual Fusion (Haematopathology)	–	LPS 033	81
19p13.3/11q23.3	MLL/MLLT1 Translocation, Dual Fusion	–	RU-LPH 082*	49
19p13.2	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	1q25/19p13	LPS 047	94
19p13.3	E2A (TCF3) Breakapart	–	LPH 019	31

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19p13.3/1q23.3	E2A (TCF3)/PBX1 Translocation, Dual Fusion	–	LPH 079	32
19p13.3/1q23.3/17q22	E2A/PBX1/HLF Translocation, Dual Fusion	–	LPH 080	33
19q13.33	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	1q25/19p13	LPS 047	94
20q12/14q32.33	IGH/MAFB *Plus* Translocation, Dual Fusion	–	LPH 077	44
20q12/20q13.1	Del(20q) Deletion	–	LPH 020	30
20q13.1/20q12	Del(20q) Deletion	–	LPH 020	30
20q13.2	ZNF217 Amplification	DEFB128	LPS 005	119
21q22.1	AML1 (RUNX1) Breakapart	–	LPH 027	13
21q22.1/12p13.2	TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion	20qter	LPH 012	62
21q22.1/8q21.3	AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion	–	LPH 026	14
21q22.13-q22.2/21q22.2-q22.3	TMPRSS2/ERG Deletion/Breakapart	ERG	LPS 021	117
21q22.13-q22.2/22q12.1-q12.2	EWSR1/ERG Translocation, Dual Fusion	–	LPS 008	101
21q22.2-q22.3/21q22.13-q22.2	TMPRSS2/ERG Deletion/Breakapart	ERG (21q22.2)	LPS 021	117
22q11.21-q11.23	IGL Breakapart	–	LPH 033	46
22q11.21-q11.23	IGL Breakapart (Haematopathology)	–	LPS 039	85
22q11.2/22q13.3	DiGeorge TBX1 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 014	131
22q11.2/22q13.3	DiGeorge/VCFS N25 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 010	131
22q11.2/22q13.3	DiGeorge/VCFS TUPLE1 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 004	130
22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Translocation, Dual Fusion	–	LPH 007	17
22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Plus Translocation, Dual Fusion	–	LPH 038	18
22q12.1-q12.2	EWSR1 Breakapart	–	LPS 006	100
22q12.1-q12.2/11q24.3	FLI1/EWSR1 Translocation, Dual Fusion	–	LPS 007	102
22q12.1-q12.2/21q22.13-q22.2	EWSR1/ERG Translocation, Dual Fusion	–	LPS 008	101
22q13.3/22q11.2	DiGeorge TBX1 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 014	131
22q13.3/22q11.2	DiGeorge/VCFS N25 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 010	131
22q13.3/22q11.2	DiGeorge/VCFS TUPLE1 & 22q13.3 Deletion Syndrome Probe Combination	–	LPU 004	130
Xp11.23	TFE3 Breakapart	–	RU-LPS 051*	116
Xp22.33/Yp11.32	CRLF2 Breakapart	–	RU-LPH 085*	24
Xp22.33/Yp11.32	SHOX	DXZ1, DYZ1	LPU 025	135
Xp22.33/Yp11.32	P2RY8 Deletion	–	RU-LPH 086*	24
Xp22.31	Kallmann (KAL1) & Steroid Sulphatase Deficiency (STS) Probe Combination	DXZ1	LPU 016	132
Xp11.1-q11.1/Yp11.1-q11.1	Dual labelled Satellite Probe Set XYc	–	LPE 0XYc	144
Xp11.1-q11.1/Yq12	Dual labelled Satellite Probe Set XYq	–	LPE 0XYq	144
Yp11.31	SRY	DXZ1, DYZ1	LPU 026	137
Yp11.32/Xp22.33	CRLF2 Breakapart	–	RU-LPH 085*	24

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ABL1	9q34.11-q34.12	BCR/ABL (ABL1) Translocation Dual Fusion	LPH 007	17
		BCR/ABL (ABL1) *Plus* Translocation Dual Fusion	LPH 038	18
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
AFF1	4q21.3-q22.1	MLL (KMT2A)/AFF1 Translocation, Dual Fusion	LPH 081	48
ALK	2p23.2-p23.1	ALK Breakapart	LPS 019	95
ANGPTL1	1q25.2	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	LPS 047	94
ANOS1 (KAL1)	Xp22.31	Kallmann (KAL1) Region/STS Region	LPU 016	132
ASS1	9q34.12	BCR/ABL (ABL1) Translocation, Dual Fusion	LPH 007	17
ATM	11q22.3	ATM Deletion	LPH 011	15
		P53 (TP53)/ATM Probe Combination	LPH 052	54
		CLL PROFILER Kit	LPH 067	21
		CLL Plus Screening Panel	LPH 087	22
		Chromoprobe Multiprobe® CLL	PMP 01x	70
BCL2	18q21.33	BCL2 Breakapart (Haematopathology)	LPS 028	77
		IGH/BCL2 *Plus* Translocation, Dual Fusion	LPH 071	38
		IGH/BCL2 Translocation, Dual Fusion (Haematopathology)	LPS 033	81
		Chromoprobe Multiprobe® CLL	PMP 01x	70
BCL6	3q27.3	BCL6 Breakapart	LPH 035	16
		BCL6 Breakapart (Haematopathology)	LPS 029	78
BCR	22q11.23	BCR/ABL (ABL1) Translocation Dual Fusion	LPH 007	17
		BCR/ABL (ABL1) *Plus* Translocation Dual Fusion	LPH 038	18
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
CBFB	16q22	CBFß/MYH11 Translocation, Dual Fusion	LPH 022	19
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
CCND1	11q13.3	CCND1 Breakapart (Haematopathology)	LPS 030	79
		IGH/CCND1 *Plus* Translocation, Dual Fusion	LPH 072	39
		IGH/CCND1 Translocation, Dual Fusion (Haematopathology)	LPS 031	82
		Chromoprobe Multiprobe® CLL	PMP 01x	70
		IGH/MYEOV *Plus*	LPH 078	45
CCND3	6p21.1	IGH/CCND3 *Plus* Translocation, Dual Fusion	LPH 075	40
CDKN2A	9p21.3	P16 (CDKN2A) Deletion	LPH 009	52
		P16 (CDKN2A) Deletion (Haematopathology)	LPS 036	88
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
CDKN2C	1p32.3	CKS1B/CDKN2C (P18) Amplification/Deletion	LPH 039	20
CELF2	10p14	DiGeorge II (10p14)	LPU 015	129
CHD5	1p36.31	SRD (CHD5) Deletion	LPS 010	114
CHIC2	4q12	FIP1L1/CHIC2/PDGFRA Deletion/Fusion	LPH 032	35
CKS1B	1q21.3	CKS1B/CDKN2C(P18) Amplification/Deletion	LPH 039	20
CRLF2	Yp11.32/Xp22.33	CRLF2 Breakapart	RU-LPH 085*	24
DLEU1	13q14.2-14.3	D13S319 *Plus* Deletion	LPH 068	25
		D13S319/13qter/12cen Deletion/Enumeration	LPH 066	25
		13q14.3	LPH 006	25
		CLL PROFILER Kit	LPH 067	21
		CLL Plus Screening Panel	LPH 087	22
		Chromoprobe Multiprobe® CLL	PMP 01x	70
DLEU2	13q14.2-14.3	D13S319 *Plus* Deletion	LPH 068	25

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		D13S319/13qter/12cen Deletion/Enumeration	LPH 066	25
		13q14.2	LPH 006	25
		CLL PROFILER Kit	LPH 067	21
		CLL *Plus* Screening Panel	LPH 087	22
		Chromoprobe Multiprobe® CLL	PMP 01x	70
DLEU7	13q14.3	D13S25 Deletion	LPH 043	25
DDIT3	12q13.3	CHOP (DDIT3) Breakapart	LPS 015	96
EGFR	7p11.2	EGFR Amplification	LPS 003	98
EGR1	5q31.2	Del(5q) Deletion	LPH 024	28
ELN	7q11.23	Williams-Beuren	LPU 011	138
	7q11.23	Saethre-Chotzen/Williams-Beuren Combination	LPU 024	134
EML4	2p21	EML4 Breakapart	LPS 020	99
ERBB2	17q12	HER2 (ERBB2) Amplification	LPS 001	106
ERG	21q22.13-q22.2	TMPRSS2/ERG Deletion/Breakapart	LPS 021	117
ETV6	12p13.2	TEL/AML1 (EVT6/RUNX1) Translocation, Dual Fusion	LPH 012	62
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
EWSR1	22q12.1-q12.2	EWSR1 Breakapart	LPS 006	100
		FLI1/EWSR1 Translocation, Dual Fusion	LPS 007	102
		EWSR1/ERG Translocation, Dual Fusion	LPS 008	101
FGFR1	8p11.23-p11.22	FGFR1 Breakapart/Amplification	LPS 018	103
FGFR3	4p16.3	IGH/FGFR3 *Plus* Translocation, Dual Fusion	LPH 074	42
FIP1L1	4q12	FIP1L1/CHIC2/PDGFRA Deletion/Fusion	LPH 032	35
FLI1	11q24.3	FLI1/EWSR1 Translocation, Dual Fusion	LPS 007	102
FOXO1	13q14.1	FOXO1 Breakapart	LPS 049	104
FUS	16p11.2	FUS Breakapart	LPS 050	105
GLTSCR1 (BICRA)/ GLTSCR2 (NOP53)	19q13.33	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	LPS 047	94
HIRA (TUPLE1)	22q11.2	DiGeorge/VCFS TUPLE1 & 22q13.3 Deletion Syndrome Probe Combinations	LPU 004	130
HLF	17q22	E2A (TCF3)/PBX1 *Plus* Translocation, Dual Fusion	LPH 080	33
IGH	14q32.3	IGH Breakapart	LPH 014	36
		IGH Plus Breakapart	LPH 070	37
		IGH Breakapart (Haematopathology)	LPS 032	80
		IGH/BCL2 *Plus* Translocation, Dual Fusion	LPH 071	38
		IGH/BCL2 Translocation, Dual Fusion (Haematopathology)	LPS 033	81
		IGH/CCND1 *Plus* Translocation, Dual Fusion	LPH 072	39
		IGH/CCND1 Translocation, Dual Fusion (Haematopathology)	LPS 031	82
		IGH/CCND3 *Plus* Translocation, Dual Fusion	LPH 075	40
		IGH/cMYC (MYC) *Plus* Translocation, Dual Fusion	LPH 076	41
		IGH/FGFR3 *Plus* Translocation, Dual Fusion	LPH 074	42
		IGH/MAF *Plus* v2 Translocation, Dual Fusion	LPH 108	43
		IGH/MAFB *Plus* Translocation, Dual Fusion	LPH 077	44
		IGH/MALT1 Translocation, Dual Fusion (Haematopathology)	LPS 034	83
		IGH/MYC Translocation, Dual Fusion (Haematopathology)	LPS 035	84
		IGH/MYEOV *Plus* Translocation, Dual Fusion	LPH 078	45
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
		Chromoprobe Multiprobe® CLL	PMP 01x	70
IGK	2p11.2	IGK Breakapart	LPH 034	46
		IGK Breakapart (Haematopathology)	LPS 038	85

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IGL	22q11.21-q11.23	IGL Breakapart	LPH 033	46
		IGL Breakapart (Haematopathology)	LPS 039	85
KMT2A	11q23.3	MLL (KMT2A) Breakapart	LPH 013	47
		MLL (KMT2A)/AFF1 Translocation, Dual Fusion	LPH 081	48
		MLL(KMT2A)/MLLT1 Translocation, Dual Fusion	RU-LPH 082*	49
		MLL(KMT2A)/MLLT3 Translocation, Dual Fusion	RU-LPH 083*	50
		MLL (KMT2A) /MLLT4 (AFDN) Translocation, Dual Fusion	RU-LPH 084*	50
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
MAF	16q23	IGH/MAF *Plus* v2 Translocation, Dual Fusion	LPH 108	43
MAFB	20q12	IGH/MAFB *Plus* Translocation, Dual Fusion	LPH 077	44
MALT1	18q21.31-q21.32	MALT1 Breakapart	LPS 017	86
		IGH/MALT1 Translocation, Dual Fusion (Haematopathology)	LPS 034	83
MDM2	12q15	MDM2 Amplification	LPS 016	107
MECOM	3q26.2	EVI1 (MECOM) Breakapart	LPH 036	34
MET	7q31.2	C-MET (MET) Amplification	LPS 004	97
MLLT1	19p13.3	MLL (KMT2A)/MLLT1 Translocation, Dual Fusion	RU-LPH 082*	49
MLLT3	9p21.3	MLL (KMT2A)/MLLT3 Translocation, Dual Fusion	RU-LPH 083*	50
MLLT4 (AFDN)	6q27	MLL (KMT2A)/MLLT4 (AFDN) Translocation, Dual Fusion	RU-LPH 084*	50
MYB	6q23.3	MYB Deletion	LPH 016	51
		CLL *Plus* Screening Panel	LPH 087	22
		Chromoprobe Multiprobe CLL	PMP 01x	68
MYBL2	20q13.1	Del(20q) Deletion	LPH 020	30
MYC	8q24.21	cMYC (MYC) Breakapart	LPH 010	23
		MYC Breakapart (Haematopathology)	LPS 027	87
		IGH/cMYC (MYC) *Plus* Translocation, Dual Fusion	LPH 076	41
		IGH/MYC Translocation, Dual Fusion (Haematopathology)	LPS 035	84
		Chromoprobe Multiprobe ALL v2	PMP 03x	70
MYCN 2	2p24.3	N-MYC (MYCN) Amplification	LPS 009	108
MYEOV	11q13.3	IGH/MYEOV *Plus* Translocation, Dual Fusion	LPH 078	45
MYH11	16p13.1	CBFβ/MYH11 Translocation, Dual Fusion	LPH 022	19
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
NSD1	5q35.2-q35.3	Cri-du-chat & Sotos Probe Combination	LPU 013	128
NSD2 (MMSET)	4p16.3	Wolf-Hirschhorn	LPU 009	129
	4p16.3	IGH/FGFR3	LPH 074	42
P2RY8	Yp11.32/Xp22.33	P2RY8 Deletion	RU-LPH 086*	24
PAX3	2q36.1	PAX3 Breakapart	LPS 012	109
PAX7	1p36.13	PAX7 Breakapart	LPS 013	109
PBX1	1q23.3	E2A/PBX1 Translocation, Dual Fusion	LPH 079	32
		E2A (TCF3)/PBX1 *Plus* Translocation, Dual Fusion	LPH 080	33
PDGFRA	4q12	FIP1L1/CHIC2/PDGFRA Deletion/Fusion	LPH 032	35
PDGFRB	5q32	PDGFRB Breakapart	LPH 031	55
PML	15q24.1	FAST PML/RARa (RARA) Translocation, Dual Fusion	LPH 064	56
		PML/RARa (RARA) Translocation, Dual Fusion	LPH 023	57
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
PTPRT	20q12/20q13.1	Del(20q) Deletion	LPH 020	30
RAI1	17p11.2	Smith-Magenis (RAI1)/Miller-Dieker Probe Combination	LPU 019	136
RARA	17q21.1-q21.2	FAST PML/RARα (RARA) Translocation, Dual Fusion	LPH 064	56

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		PML/RARα (RARA) Translocation, Dual Fusion	LPH 023	57
		RARα (RARA) Breakapart	LPH 065	58
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
RELN	7q22	Del(7q) Deletion	LPH 025	29
RB1	13q14.2	RB1 Deletion	LPS 011	90
RET	10q11.21	RET Breakapart	LPS 045	111
ROS1	6q22.1	ROS1 Breakapart	LPS 022	112
		ROS1 *Plus* Breakapart	LPS 046	113
RUNX1	21q22.1	AML1 (RUNX1) Breakapart	LPH 027	13
		AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion	LPH 026	14
		TEL/AML1 (ETV6/RUNX1) Translocation, Dual Fusion	LPH 012	62
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
RUNX1T1	8q21.3	AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion	LPH 026	14
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
SHOX	Xp22.33/Yp11.32	SHOX	LPU 025	135
SNRPN	15q11.2	Prader-Willi/Angelman (SNRPN)	LPU 005	133
SRY	Yp11.31	SRY	LPU 026	137
SS18	18q11.2	SYT (SS18) Breakapart	LPS 014	115
STS	Xp22.31	Kallmann (KAL1) & Steroid Sulphatase Deficiency (STS) Probe Combination	LPU 016	132
TBX1	22q11.21	DiGeorge TBX1 & 22q13.3 Deletion Syndrome Probe Combination	LPU 014	131
TCF3	19p13.3	E2A (TCF3) Breakapart	LPH 019	136
		E2A (TCF3) /PBX1 Translocation, Dual Fusion	LPH 079	32
		E2A (TCF3) /PBX1 *Plus* Translocation, Dual Fusion	LPH 080	33
		Chromoprobe Multiprobe® ALL v2	PMP 03x	68
TCL1 A/B	14q32.13-q32.2	TCL1 Breakapart	LPH 046	59
TFE3	Xp11.23	TFE3 Breakapart	RU-LPS 051*	116
TLX1	10q24.31	TLX1 Breakapart	LPH 049	63
TLX3	5q35.1	TLX3 Breakapart	LPH 050	64
TMPRSS2	21q22.2-q22.3	TMPRSS2/ERG Deletion/Breakapart	LPS 021	117
TOP2A	17q21.2	TOP2A Amplification/Deletion	LPS 002	118
TP53	17p13	P53 (TP53) Deletion	LPH 017	53
		P53 (TP53) Deletion (Haematopathology)	LPS 037	89
		P53 (TP53)/ATM Probe Combination	LPH 052	54
		CLL PROFILER Kit	LPH 067	21
		CLL Plus Screening Panel	LPH 087	22
		Chromoprobe Multiprobe® AML/MDS	PMP 02x	72
		Chromoprobe Multiprobe® CLL	PMP 01x	70
TP73	1p36.32	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	LPS 047	94
TRA	14q11.2	TCRAD Breakapart	LPH 047	60
TRB	7q34	TCRB (TRB) Breakapart	LPH 048	61
TRD	14q11.2	TCRAD Breakapart	LPH 047	60
TWIST1	7p21.1	Saethre-Chotzen/Williams-Beuren Combination	LPU 024	134
UBE2QL1	5p15.31	Cri-du-chat & Sotos Probe Combination	LPU 013	128
UBE3A	15q11.2-q12	Angelman (UBE3A/D15S10)	LPU 006	127
ZNF217	20q13.2	ZNF217 Amplification	LPS 005	119
ZNF443	19p13.2	1p36/1q25 and 19q13/19p13 Deletion Probe Kit	LPS 047	94

* For research use only, not for use in diagnostic procedures.

Pathology Products by Disease State*

Malignancy	Chromosome Region	Cytocell Products	Cat. No.	Page
Brain Tumor	9p21.3	P16 (CDKN2A) Deletion	LPS 036	88
Breast Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97
	11q13.3	CCND1 Breakapart	LPS 030	79
	7p11.2	EGFR Amplification	LPS 003	98
	8p11.23-p11.22	FGFR1 Breakapart/Amplification	LPS 018	103
	17q12	HER2 (ERBB2) Amplification	LPS 001	106
	13q14.2	RB1 Deletion	LPS 011	90
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
	17q21.2	TOP2A Amplification/Deletion	LPS 002	118
	20p13/20q13.2	ZNF217 Amplification	LPS 005	119
Cholangiocarcinoma (Bile duct)	6q22.1	ROS1 Breakapart	LPS 022	112
Colorectal Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97
	7p11.2	EGFR Amplification	LPS 003	98
	12q15	MDM2 Amplification	LPS 016	107
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Gallbladder Cancer	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Gastric Cancer	11q13.3	CCND1 Breakapart	LPS 030	79
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Glioma	1p36.32/1q25; 19q13.3/19p13.2	1p36/1q25 and 19q13/19p13 Deletion	LPS 047	94
	12q15	MDM2 Amplification	LPS 016	107
	6q22.1	ROS1 Breakapart	LPS 022	112
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Laryngeal	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Lung Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97
	17q12	HER2 (ERBB2) Amplification	LPS 001	106
	2p23.2-p23.1	ALK Breakapart	LPS 019	95
	2p21	EML4 Breakapart	LPS 020	99
	10q11.21	RET Breakapart	LPS 045	111
	6q22.1	ROS1 Breakapart	LPS 022	112
	6q22.1	ROS1 *Plus* Breakapart	LPS 046	113
	7p11.2	EGFR Amplification	LPS 003	98
	9p21.3	P16 (CDKN2A) Deletion	LPS 036	88
	13q14.2	RB1 Deletion	LPS 011	90
	8p11.23-p11.22	FGFR1 Breakapart/Amplification	LPS 018	103
	12q15	MDM2 Amplification	LPS 016	107
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Lymphoma	18q21.33-q22.1	BCL2 Breakapart	LPS 028	77
	3q27.3-q28	BCL6 Breakapart	LPS 029	78
	11q13.3	CCND1 Breakapart	LPS 030	79
	14q32.33	IGH Breakapart	LPS 032	80
	14q32.3/18q21.33-q22.1	IGH/BCL2 Translocation	LPS 033	81
	14q32.3/11q13.3	IGH/CCND1 Translocation	LPS 031	82
	14q32.3/18q21.31-q21.32	IGH/MALT1 Translocation	LPS 034	83
	14q32.3/8q24.21	IGH/MYC Translocation	LPS 035	84
	2p11.2	IGK Breakapart	LPS 038	85

*As supported by literature.

Pathology Products by Disease State*

Malignancy	Chromosome Region	Cytocell Products	Cat. No.	Page
	22q11.21-q11.23	IGL Breakapart	LPS 039	85
	18q21.31-q21.32	MALT1 Breakapart	LPS 017	86
	8q24.21	MYC Breakapart	LPS 027	87
	9p21.3	P16 (CDKN2A) Deletion	LPS 036	88
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
	17p13	P53 (TP53) Deletion	LPS 037	89
Medulloblastoma	2p24.3/2q11.2	N-MYC (MYCN) Amplification	LPS 009	108
Neuroblastoma	2p24.3/2q11.2	N-MYC (MYCN) Amplification	LPS 009	108
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
Oesophageal Cancer	12q15	MDM2 Amplification	LPS 016	107
Ovarian Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97
	17q12	HER2 (ERBB2) Amplification	LPS 001	106
	6q22.1	ROS1 Breakapart	LPS 022	112
	1p36.31	SRD (CHD5) Deletion	LPS 010	114
	17q21.2	TOP2A Amplification/Deletion	LPS 002	118
	20p13/20q13.2	ZNF217 Amplification	LPS 005	119
Pancreatic Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97
Prostate Cancer	1p36.31	SRD (CHD5) Deletion	LPS 010	114
	21q22.2-q22.2/21q22.13-q22.2	TMPRSS2/ERG Deletion/Breakapart	LPS 021	117
	20q13.2	ZNF217 Amplification	LPS 005	119
Retinoblastoma	2p24.3/2q11.2	N-MYC (MYCN) Amplification	LPS 009	108
	13q14.2	RB1 Deletion	LPS 011	90
Sarcoma	7q31.2	c-MET (MET) Amplification	LPS 004	97
	12q13.3	CHOP (DDIT3) Breakapart	LPS 015	96
	22q12.1-q12.2	EWSR1 Breakapart	LPS 006	100
	22q12.1-q12.2/21q22.13-q22.2	EWSR1/ERG Translocation	LPS 008	101
	11q24.3/22q12.1-q12.2	FLI1/EWSR1 Translocation	LPS 007	102
	13q14.1	FOXO1 Breakapart	LPS 049	104
	16p11.2	FUS Breakapart	LPS 050	105
	12q15	MDM2 Amplification	LPS 016	107
	2p36.1	PAX3 Breakapart	LPS 012	109
	1p36.13	PAX7 Breakapart	LPS 013	109
	18q11.2	SYT (SS18) Breakapart	LPS 014	115
	20p13/20q13.2	ZNF217 Amplification	LPS 005	119
Thyroid Cancer	7q31.2	C-MET (MET) Amplification	LPS 004	97

*As supported by literature.

Haematology Products by Disease State*

Haematological malignancy	Chromosome Region	Cytocell Products	Cat. No.	Page
ALL Acute Lymphoblastic Leukaemia (ALL)	21q22.12	AML1 (RUNX1) Breakapart	LPH 027	13
	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Translocation	LPH 007	17
	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) *Plus* Translocation	LPH 038	18
	19p13.3	E2A (TCF3) Breakapart	LPH 019	31
	19p13.3/1q23.3	E2A (TCF3)/PBX1 Translocation	LPH 079	32
	19p13.3/1q23.3/17q22	E2A (TCF3)/PBX1 *Plus* Translocation	LPH 080	33
	14q32.3	IGH Breakapart	LPH 014	36
	14q32.3	IGH Plus Breakapart	LPH 070	37
	11q23.3	MLL (KMT2A) Breakapart	LPH 013	47
	11q23.3/4q21.3-q22.1	MLL (KMT2A)/AFF1 Translocation	LPH 081	48
	6q23.3	MYB Deletion	LPH 016	51
	5q32	PDGFRB Breakapart	LPH 031	55
	9p21.3	P16 (CDKN2A) Deletion	LPH 009	52
	17p13.1	P53 (TP53) Deletion	LPH 017	53
	14q32.13-q32.2	TCL1 Breakapart	LPH 046	59
	14q11.2	TCRAD Breakapart	LPH 047	60
	7q34	TCRB (TRB) Breakapart	LPH 048	61
	21q22.1	TEL/AML1 (ETV6/RUNX1) Translocation	LPH 012	62
	10q24.31	TLX1 Breakapart	LPH 049	63
	5q35.1	TLX3 Breakapart	LPH 050	64
AML Acute Myeloid Leukaemia (AML)	21q22.1	AML1 (RUNX1) Breakapart	LPH 027	13
	21q22.1/8q21.3	AML1/ETO (RUNX1/RUNX1T1) Translocation	LPH 026	14
	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Translocation	LPH 007	17
	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) *Plus* Translocation	LPH 038	18
	16q22/16p13.1	CBFβ (CBFB)/MYH11	LPH 022	19
	5p15.3/5q31.2	Del(5q) Deletion	LPH 024	28
	7q22/7q31.2	Del(7q) Deletion	LPH 025	29
	20q12/20q13.1	Del(20q) Deletion	LPH 020	30
	3q26.2	EVI1 (MECOM) Breakapart	LPH 036	34
	11q23.3	MLL (KMT2A) Breakapart	LPH 013	47
	11q23.3/4q21.3-q22.1	MLL (KMT2A)/AFF1 Translocation	LPH 081	48
	17p13	P53 (TP53) Deletion	LPH 017	53
	15q24.1/17q21.1-q21.2	FAST PML/RARα (RARA) Translocation	LPH 064	56
	15q24.1/17q21.1-q21.2	PML/RARα (RARA) Translocation	LPH 023	57
	17q21.1-q21.2	RARα (RARA) Breakapart	LPH 065	58
CLL Chronic Lymphocytic Leukaemia (CLL)	13q14.2-q14.3	13q14.3 Deletion	LPH 006	25
	12p11.1-q11.1	Alpha Satellite 12 *Plus* for CLL	LPH 069	12
	11q22.3	ATM Deletion	LPH 011	15
	13q14.3	D13S25 Deletion	LPH 043	25
	13q14.2-q14.3	D13S319 *Plus* Deletion	LPH 068	25

*As supported by literature.

Haematology Products by Disease State*

Haematological malignancy	Chromosome Region	Cytocell Products	Cat. No.	Page
	13q14.2-q14.3/13q34/12CEN	D13S319/13qter/12cen Deletion/ Enumeration	LPH 066	27
	14q32.3	IGH Breakapart	LPH014	36
	14q32.3	IGH *Plus* Breakapart	LPH 070	37
	14q32.3/18q21.33	IGH/BCL2 *Plus* Translocation	LPH 071	38
	6q23.3	MYB Deletion	LPH 016	51
	17p13	P53 (TP53) Deletion	LPH 017	53
	17p13/11q22.3	P53 (TP53)/ATM Probe Combination	LPH 052	54
	Various	CLL PROFILER Kit	LPH 067	21
	Various	CLL *Plus* Screening Panel	LPH 087	22
CML **Chromic Myeloid Leukaemia (CML)**	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Translocation	LPH 007	17
	22q11.22-q11.23/9q34.11-q34.12	BCR/ABL (ABL1) Plus Translocation	LPH 038	18
MDS **Myelodysplastic Syndrome (MDS)**	5p15.3/5q31.2	Del(5q) Deletion	LPH 024	28
	7q22/7q31.2	Del(7q) Deletion	LPH 025	29
	20q12/20q13.1	Del(20q) Deletion	LPH 020	30
	3q26.2	EVI1 (MECOM) Breakapart	LPH 036	34
	11q23.3	MLL (KMT2A) Breakapart	LPH 013	47
	17p13	P53 (TP53) Deletion	LPH 017	53
MPN **Myeloproliferative Neoplasm (MPN)**	4q12	FIP1L1/CHIC2/PDGFRA Deletion/ Fusion	LPH 032	35
	5q32	PDGFRB Breakapart	LPH 031	55
L **Lymphoma (L)**	3q27.3	BCL6 Breakapart	LPH 035	16
	8q24.21	cMYC (MYC) Breakapart	LPH 010	23
	14q32.3	IGH Breakapart	LPH 014	36
	14q32.3	IGH Plus Breakapart	LPH 070	37
	14q32.3/18q21.33	IGH/BCL2 *Plus* Translocation	LPH 071	38
	14q32.3/11q13.3	IGH/CCND1 *Plus* Translocation	LPH 072	39
	14q32.3/8q24.21	IGH/cMYC (MYC) *Plus* Translocation	LPH 076	41
	14q32.3/11q13.3	IGH/MYEOV *Plus*	LPH 078	45
	2p11.2	IGK Breakapart	LPH 034	46
	22q11.21-q11.23	IGL Breakapart	LPH 033	46
	6q23.3	MYB Deletion	LPH 016	51
	9p21.3	P16 (CDKN2A)	LPH 009	52
	17p13	P53 (TP53) Deletion	LPH 017	53
MM **Multiple Myeloma (MM)**	13q14.2-q14.3	13q14.3 Deletion	LPH 006	25
	1q21.3/1p32.3	CKS1B/CDKN2C (P18) Amplification/Deletion	LPH 039	20
	13q14.3	D13S25 Deletion	LPH 043	25
	13q14.2-q14.3	D13S319 *Plus* Deletion	LPH 068	25
	14q32.3	IGH Breakapart	LPH 014	36
	14q32.3	IGH Plus Breakapart	LPH 070	37
	14q32.3/6p21	IGH/CCND3 *Plus* Translocation	LPH 075	40
	14q32.3/4p16.3	IGH/FGFR3 *Plus* Translocation	LPH 074	42
	14q32.3/16q23	IGH/MAF *Plus* v2 Translocation	LPH 108	43
	14q32.3/20q12	IGH/MAFB *Plus* Translocation	LPH 077	44
	14q32.3/11q13.3	IGH/MYEOV *Plus* Translocation	LPH 078	45
	17p13	P53 (TP53) Deletion	LPH 017	53

*As supported by literature.

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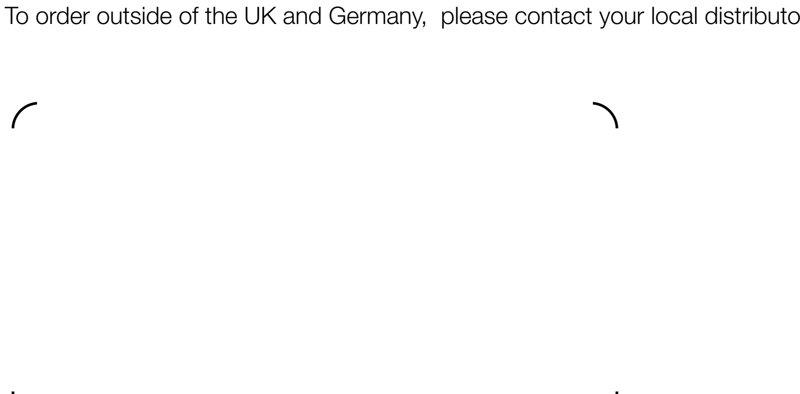

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