Clinical Background and Genetics
- Chromosome breakage disorders are a group of rare genetic conditions inherited in an autosomal recessive or X linked inheritance pattern.
- Patients with these disorders show increased predisposition to solid and haematological malignancies have a high incidence of other congenital abnormalities such as microcephaly and radial ray defects.
- The disorders are characterised by defects in DNA repair mechanisms, cell cycle control or genomic instability.
- The service is designed to support the specialist cytogenetic chromosome breakage service offered by Bristol Genetics Laboratory, further details of which are available on the laboratory website.
- The panel test includes genes known to be associated with chromosome breakage disorders, premature chromosome separation and premature centromeric separation.
- Due to the clinical overlap and complexity in diagnosis the gene panel contains genes for several key differential diagnoses e.g. radial ray abnormality syndromes.
- A full list of genes and disorders included in the panel is on page 2.

Service offered
- 63 genes are sequenced using a custom designed Agilent SureSelect Target Enrichment method; sequencing is performed on an Illumina MiSeq. Analysis is performed using an open source in-house developed pipeline (alignment: BWA; alignment modification and variant calling: GATK; variant annotation: Annovar).
- All variants reported are confirmed by Sanger sequencing
- MLPA analysis for FANCA is also available.

Referrals
- Diagnostic referrals are accepted from Consultant Clinical Geneticists, Consultant Paediatricians and Consultant Oncologists.
- It is essential that the referring clinician provides the clinical information and consent required in the pre-test pro forma (page 3) or relevant clinical letter of referral.

Quality
- BGL participates in the appropriate technical EQA schemes for Sanger and next generation sequencing.

Target reporting Time (2016/2017)
- Gene panel testing 16 weeks
- Cascade tests 14 days

Please contact the laboratory for up-to-date prices and more information on this test.
- For clinical advice please contact Dr Ruth Newbury-Ecob, Clinical Genetics, St. Michael's Hospital, Bristol, Tel: 0117 342 5653
# Chromosome Breakage Disorders NGS Gene Panel Proforma

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Consultant Name:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient postcode:</td>
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<tr>
<td>Date of Birth:</td>
<td></td>
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<tr>
<td>Sex:</td>
<td></td>
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<tr>
<td>NHS Number</td>
<td></td>
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<tr>
<td>Hospital Number:</td>
<td></td>
</tr>
</tbody>
</table>

## Fanconi Anaemia
- FANCA
- FANCB
- FANCC
- BRCA2
- FANCD2
- FANCE
- FANCF
- FANCG
- FANCl
- BRIP1
- FANCL
- PALB2
- RAD51C
- SLX4
- XRCC2

## Ataxia Telangiectasia (AT-Like)
- ATM
- MRE11A

## Ataxia with oculomotor apraxia and hypoalbuminemia
- APTX

## Xeroderma Pigmentosum
- XPA
- XPC
- ERCC1
- ERCC3
- ERCC4

## Trichothiodystrophy
- ERCC2
- MLLKP
- ERCC3
- GTF2H5

## Cockayne Syndrome
- ERCC6
- ERCC8

## Autosomal Recessive Primary Microcephaly
- MCPH1
- CDK5RAP2
- ASPM
- STIL
- WDR62

## Seckel Syndrome
- ATR
- RBBP8
- CEP152
- CENPJ

## Meier-Gorlin Syndrome
- ORC1
- ORC4
- ORC6
- CDT1
- CDC6

## Cerebro Oculo Facio Skeletal syndrome
- ERCC1
- ERCC2
- ERCC6

## Baller-Gerold/Rothmund Thomson/RAPADILINO
- RECL4

## Natural killer cell and glucocorticoid deficiency with DNA repair defect
- MCM4

## Nijmegen breakage syndrome (& NBS-like)
- NBN
- RAD50

## Werner syndrome
- WRN

## Warsaw breakage syndrome
- DDX11

## Roberts /SC phocomelia syndrome
- ESCO2

## Bloom Syndrome
- BLM

## Immunodeficiency-centromeric instability-facial anomalies syndrome
- DNMT3B

## Duane-Radial Ray & IVIC Syndrome
- SALL4

## Townes-Brocks Syndrome
- SALL1

## Holt-Oram Syndrome
- TBX5

## Ulnar-mammary syndrome
- TBX3

## TAR Syndrome
- RBM8A

## Lig4 Syndrome
- Lig4

## N Syndrome
- POLA1

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Active date of this version: 10/07/2017  
DETAILS CORRECT AT DATE OF PRINTING ONLY.  
Approved by: Laura Yarram-Smith
## Indications for testing:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if this patient meets criteria</th>
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<tbody>
<tr>
<td>Unexplained pre- and postnatal growth deficiency or failure to thrive and small stature in association with immune deficiency or cancer</td>
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<tr>
<td>Progressive cerebellar ataxia in young children</td>
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<tr>
<td>Physical features consistent with a chromosome breakage disorder e.g. limb malformations, microcephaly, growth retardation</td>
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<tr>
<td>Recurrent infections or immunodeficiency in association with microcephaly</td>
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<tr>
<td>History of leukaemia, lymphoma or solid tumour at an earlier than expected age, particularly in association with other features of chromosome breakage disorder</td>
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<tr>
<td>Increased sister chromatid exchange as detected cytogenetically, chromosomal instability or increased cellular sensitivity to ionizing radiation</td>
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<tr>
<td>Unexpected toxicity to chemotherapy or radiation therapy</td>
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<tr>
<td>Borderline increased chromosome breakage with DEB exposure.</td>
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</tbody>
</table>

## Please indicate suspected clinical diagnosis:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Tick</th>
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<tbody>
<tr>
<td>Ataxia Telangiectasia</td>
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<tr>
<td>Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia</td>
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<tr>
<td>Ataxia-telangiectasia-like disorder</td>
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<tr>
<td>Baller-Gerold syndrome</td>
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<td>Bloom Syndrome</td>
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<tr>
<td>Cerebrooculofacioskeletal syndrome 1</td>
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<td>Cerebrooculofacioskeletal syndrome 2</td>
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<tr>
<td>Cockayne syndrome</td>
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<tr>
<td>Cutaneous telangiectasia and cancer syndrome, familial</td>
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<tr>
<td>De Sanctis-Cacchione syndrome</td>
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<tr>
<td>Fanconi Anaemia</td>
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<tr>
<td>Jawad syndrome</td>
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<tr>
<td>LIG4 syndrome</td>
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<tr>
<td>Meier-Gorlin syndrome</td>
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<tr>
<td>N syndrome</td>
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<td>Natural killer cell and glucocorticoid deficiency with DNA repair defect</td>
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<tr>
<td>Nijmegen breakage syndrome</td>
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<tr>
<td>Nijmegen breakage syndrome-like disorder</td>
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<tr>
<td>Primary autosomal recessive Microcephaly</td>
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<tr>
<td>RAPADILINO syndrome</td>
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</tbody>
</table>
Roberts syndrome/ SC phocomelia syndrome
Rothmund-Thomson syndrome
Seckel syndrome
Trichothiodystrophy
UV-sensitive syndrome 2
Warsaw breakage syndrome
Werner syndrome
Xeroderma Pigmentosum
XFE Progeroid syndrome

Please detail the clinical features of this patient, including relevant haematology results:

Please note this NGS panel test includes cancer predisposition genes including BRCA2. Analysis may reveal information regarding cancer susceptibility that may have implications for this patient and other family members. It is laboratory policy to report all clinically relevant findings. Please sign below to indicate that informed consent has been obtained prior to testing. Testing will not be undertaken if this form is not signed by the referring clinician.

Signed
Print
Position