National Genomic Test Directory Haematological Oncology (HaemOnc) Eligibility Criteria

Contents Table

1. Test Package: Acute Myeloid Leukaemia TP450

Acute Myeloid Leukaemia Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

NB some M codes are just listed as GTas these tests are aligned to the simplification process

WGS tests

GT726 / M80.1 WGS Germline & Tumour - AML
GT24 / M80.57 WGS Tumour First - AML
GT802 / M80.58 WGS Follow-up Germline - AML

GT517 / M90.1 WGS Germline & Tumour - BPDCN
GT879 / M90.6 WGS Tumour First - BPDCN
GT1221 / M90.7 WGS Follow-up Germline - BPDCN

All patients (of any age i.e. paediatric, TYA and adult) with a morphological diagnosis of acute myeloid leukaemia (AML) are eligible for whole genome sequencing (WGS), primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / (RELAPSE/REFRACTORY)

Tumour and germline samples can be submitted simultaneously (i.e M80.1) or separately i.e. tumour first (M80.57) followed by a germline when/if available (M80.58). At any presentation point either M80.1 or M80.57 +/- M80.58 is permissible, however once a non-contaminated germline has been submitted (either as part of M80.1 or M80.58) this can be bioinformatically re-used as a germline if any subsequent tumour samples are submitted for WGS.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

Targeted tests

GT533 / M80.18 (*FLT3* ITD)

GT916 / M80.21 (*FLT3* TKD)
GT921 / M80.22 (*NPM1*)
GT494 / M80.23 (*IDH1*)
GT649 *BCR::ABL1*-multiplex

- For patients with a morphological diagnosis of AML at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria [*NPM1*]. DIAGNOSIS
- For patients with a morphological diagnosis of acute myeloid leukaemia with concerns it had evolved from background chronic myeloid leukaemia. DIAGNOSIS
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification for allogeneic haematopoietic stem cell transplant if appropriate [*NPM1, FLT3* ITD]. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors) [*NPM1, FLT3* ITD*, FLT3* TKD*, IDH1*]. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML receiving/received targeted inhibitor treatment where assessment of disease response at a molecular level may influence the subsequent treatment strategy [*FLT3* ITD*, FLT3* TKD*, IDH1*]. (NB the detection limits of any assay used for this testing indication should be considered when determining how informative such testing is).

Small variant / copy number detection via panel

GT253 / M80.2 (NGS small variant panel)
GT629 / M80.53 (NGS copy number variant panel – to be delivered in conjunction with the NGS small variant panel. NB It is envisaged that any copy number variant [CNV] panel will have a SNP backbone or similar, therefore allowing detection of CNVs across the genome as opposed to be limited to the target regions in the test directory)

- For patients with a morphological diagnosis of AML at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification for allogeneic haematopoietic stem cell transplant if appropriate. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory to inform treatment (may include conventional

chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELAPSE/REFRACTORY

- For patients with a morphological diagnosis of AML receiving/received curative intent treatment where assessment of disease response at a molecular level may influence the subsequent treatment strategy (NB to use an NGS assay for this purpose it must be of suitable sensitivity/sequencing depth to be informative and it should be noted that a standard depth NGS panel is not a formal measurable residual disease [MRD] assay). It is expected that using this test for this indication will be the exception rather than the norm. MONITORING DURING / POST-TREATMENT

Global copy number +/- structural variant via cytogenetics

GT1096 / M80.3 (Karyotype)
GT17 (SNP array) – used as a salvage test in the event of insufficient metaphases being available for karyotype analysis.

- For patients with a morphological diagnosis of AML at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. NB SNP array would typically be used in the event of karyotype failure rather than as a first-line diagnostic test. DIAGNOSIS
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification for allogeneic haematopoietic stem cell transplant if appropriate. NB SNP array would typically be used in the event of karyotype failure rather than as a first-line diagnostic test. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens or targeted inhibitors). NB SNP array would typically be used in the event of karyotype failure rather than as a first-line diagnostic test. DIAGNOSIS / RELAPSE/REFRACTORY

Targeted copy number +/- structural variant via FISH / RT-PCR

M80.5, M80.25- M80.40, M80.54 (Individual FISH tests)
Replaced by GT101, GT1033, GT1064, GT112, GT116, GT1294, GT113, GT14, GT157, GT180, GT258, GT275, GT289, GT61, GT656, GT700, GT716, GT74 (see excel spreadsheet for individual test mapping)
M80.7, M80.41-M80.52 (Individual RT-PCR tests) non-quantitative
Replaced by GT351 (see excel spreadsheet for individual test mapping)

- For patients with a morphological diagnosis of AML at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. The specific identify of

FISH / RT-PCR targets should correlate with national guidelines (e.g. BSH Good Practice Paper: https://doi.org/10.1111/bjh.18516) and will reflect local testing strategy in order to meet nationally mandated genomic turn-around-times (TATs). It is expected that FISH / RT-PCR testing will not duplicate other structural / copy number variant testing unless required to meet rapid TATs. DIAGNOSIS

- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification for allogeneic haematopoietic stem cell transplant if appropriate. The specific identify of FISH / RT-PCR targets should correlate with national guidelines (e.g. BSH Good Practice Paper: https://doi.org/10.1111/bjh.18516) and will reflect local testing strategy in order to meet nationally mandated genomic turn-around-times (TATs). It is expected that FISH / RT-PCR testing will not duplicate other structural / copy number variant testing unless required to meet rapid TATs. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). The specific identify of FISH / RT-PCR targets should correlate with national guidelines (e.g. BSH Good Practice Paper: https://doi.org/10.1111/bjh.18516) and will reflect local testing strategy in order to meet nationally mandated genomic turn-around-times (TATs). It is expected that FISH / RT-PCR testing will not duplicate other structural / copy number variant testing unless required to meet rapid TATs. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML receiving/received treatment where assessment of disease response at this level of sensitivity (i.e. detection by FISH – see below for formal RT-qPCR MRD testing) may influence the subsequent treatment strategy. MONITORING DURING / POST-TREATMENT

Structural variant detection via NGS panel

GT185 / M80.8 (NGS Structural variant panel)

- For patients with a morphological diagnosis of AML at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as karyotype and NGS small variant panel if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of

a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology. DIAGNOSIS

- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification for allogeneic haematopoietic stem cell transplant if appropriate. It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as karyotype and NGS small variant panel if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as karyotype and NGS small variant panel if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology. DIAGNOSIS / RELAPSE/REFRACTORY
- For patients with a morphological diagnosis of AML at diagnosis for whom a curative approach is being pursued to identify an appropriate target for formal measurable residual disease (MRD) monitoring. It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as karyotype and NGS small variant panel if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology. DIAGNOSIS

Resistance mutation testing

GT303 / M80.15 (*BCR::ABL1* TKD variant testing)

- For patients with a morphological diagnosis of AML known to have a *BCR::ABL1* rearrangement whose response to a targeted inhibitor is such that there is clinical suspicion that there may be a resistance variant within the *ABL1* tyrosine kinase domain. NB this assay should have a minimum variant allele frequency level of detection of 5% (i.e. 5% of

the *BCR::ABL1* transcripts need to bear the variant). MONITORING DURING TREATMENT

Measurable residual disease testing

GT1062 / M80.9 (*NPM1* MRD)
GT1228 / M80.56 (Rare *NPM1* transcript MRD)
GT475 / M80.10 (*PML::RARA* MRD)
GT343 / M80.11 (*RUNX1::RUNX1T1* MRD)
GT870 / M80.12 (*CBFB::MYH11* MRD)
GT31 / M80.13 (*BCR::ABL1* MRD)
GT673 / M80.55 (Rare *BCR::ABL1* MRD)
GT703 / M80.14 (Other MRD)

- For patients with a morphological diagnosis of AML, known to have the specific described genomic aberration of the assay, receiving/received curative treatment where assessment of disease response at a measurable residual disease [MRD] level may influence the subsequent treatment strategy. The frequency of such monitoring should follow any available national guidelines or otherwise be concentrated at points where knowledge of the transcript level has the potential to influence treatment strategy. MONITORING DURING / POST-TREATMENT

  These eligibility criteria pertain only to acquired genomic abnormalities. Information regarding eligibility for germline testing in the context of AML (including predictive testing of potential carriers) is available in the rare disease test directory.

2. Test Package: Myelodysplastic Syndromes TP202

Myelodysplastic syndrome (including myelodysplastic / myeloproliferative neoplasms & hypoplastic MDS/ aplastic anaemia differential) Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT1312 / M82.6 WGS Germline & Tumour - MDS
GT1439 / M82.22 WGS Tumour First - MDS
GT1023 / M82.23 WGS Follow-up Germline - MDS

GT1382 / M83.4 WGS Germline & Tumour - Aplastic Anaemia
GT1340 / M83.5 WGS Tumour First - Aplastic Anaemia
GT304 / M83.6 WGS Follow-up Germline - Aplastic Anaemia

GT1238 / M88.2 WGS Germline & Tumour - JMML
GT702 / M88.11 WGS Tumour First - JMML
GT1114 / M88.12 WGS Follow-up Germline - JMML

GT265 / M224.4 WGS Germline & Tumour - MDS/MPN
GT889 / M224.41 WGS Tumour First - MDS/MPN
GT128 / M224.42 WGS Follow-up Germline - MDS/MPN

NB Myelodysplasia (MDS), Juvenile myelomonocytic leukaemia (JMML), Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) will be referred to under the umbrella term of dysplastic neoplasm in the remainder of this document.

All paediatric and TYA patients with a confirmed or suspected diagnosis of a dysplastic neoplasm OR aplastic anaemia are eligible for WGS primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / (REFRACTORY)

Tumour and germline samples can be submitted simultaneously (i.e M82.6 / M83.4 / M88.2 / M224.4) or separately i.e. tumour first (M82.22 / M83.5 /

M88.11 / M224.41) followed by a germline when/if available (M82.23 / M83.6 / M88.12 / M224.42). At any presentation point either M82.6 or M82.22 +/- M82.23, M83.4 or M83.5 +/- M83.6, M88.2 or M88.11 +/- M88.12, M224.4 or M224.41 +/- M224.42 is permissible, however once a non-contaminated germline has been submitted (either as part of M82.6 / M83.4 / M88.2 / M224.4 or M82.23 / M83.6 / M88.12 / M224.42) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

For adult patients with a confirmed or suspected diagnosis of a dysplastic neoplasm or aplastic anaemia, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Small variant / copy number detection via panel

GT1297 / M82.1 (NGS small variant panel – it is envisaged that the choice of gene footprint will ensure all relevant variants including putative resistance mutations are included).
GT397 / M82.16 (NGS copy number variant panel – to be delivered in conjunction with the NGS small variant panel. NB It is envisaged that any copy number variant [CNV] panel will have a SNP backbone or similar, allowing detection of CNVs across the genome as opposed to limited to the target regions in the test directory).

- For patients with a suspected diagnosis of a dysplastic neoplasm or aplastic anaemia where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia where demonstration of a specific genomic abnormality would allow access to a targeted treatment (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have undergone a change in their disease phenotype

(e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION

- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia receiving treatment where assessment of the disease response at a molecular level may influence treatment strategy (e.g. knowledge of molecular response prior to an allogeneic haematopoietic stem cell transplant). MONITORING DURING / POST-TREATMENT
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Global copy number +/- structural variant via cytogenetics

GT1375 / M82.2 (Karyotype)
GT 635 (SNP array) – it is envisaged this will be used in line with the national SNP array guidelines i.e. particularly used as a salvage test in the event of insufficient metaphases for karyotype analysis. If this test is used in place of karyotyping, clarifications of the limitations of the technique, particularly around the inability to detect balanced translocations, should be clearly stated on the report.

- For patients with a suspected diagnosis of a dysplastic neoplasm or aplastic anaemia where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Targeted copy number +/- structural variant via FISH

M82.4, M82.7-M82.9, M82.19-20, M82.22 (Individual FISH tests)

Replaced by GT1124, GT1248, GT172, GT198, GT595, GT939, GT1302

- For patients with a suspected diagnosis of a dysplastic neoplasm or aplastic anaemia where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a dysplastic neoplasm or aplastic anaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

3. Test Package: Myeloproliferative Neoplasm TP228

Myeloproliferative Neoplasms Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT552 / M85.13 WGS Germline & Tumour - MPN
GT543 / M85.37 WGS Tumour First - MPN
GT1236 / M85.38 WGS Follow-up Germline - MPN

GT1063 / M86.3 WGS Germline & Tumour - Systemic Mastocytosis
GT12 / M86.4 WGS Tumour First - Systemic Mastocytosis
GT1029 / M86.5 WGS Follow-up Germline - Systemic Mastocytosis

All paediatric and TYA patients with a confirmed or suspected diagnosis of a myeloproliferative neoplasm are eligible for WGS, primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / (REFRACTORY)

Tumour and germline samples can be submitted simultaneously (i.e M85.13 or M86.3) or separately i.e. tumour first (M85.37 or M86.4) followed by a germline when/if available (M85.38 or M86.5). At any presentation point either M85.13 / M86.3 or M85.37 +/- M85.38 or M86.4 +/- M86.5 is permissible, however once a non-contaminated germline has been submitted (either as part of M85.13 / M86.3 or M85.38 / M86.5) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

For adult patients with a confirmed or suspected diagnosis of a myeloproliferative neoplasm, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Targeted tests

GT986 / M85.14 (*JAK2* V617F)

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm when either stand-alone *JAK2* V617F testing is appropriate (e.g. isolated polycythaemia) OR the small targeted NGS panel M85.1 (MPN multi-targeted NGS small variant panel) has failed, there is insufficient DNA to attempt this approach, or there is ambiguity in the panel result. DIAGNOSIS
- It is recognised that there is a small population of *JAK2* V617F-mutated patients who are receiving / have received disease modifying treatment where knowledge of the response of the *JAK2* V617F-mutated clone may assist in further management; in these circumstances infrequent monitoring (or repeat testing in response to a change in clinical phenotype) may be appropriate. MONITORING DURING / POST-TREATMENT

GT965 / M85.15 (*JAK2* exon 12)

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm when the small targeted NGS panel M85.1 (MPN multi-targeted NGS small variant panel) has failed, there is insufficient DNA to attempt this approach or there is ambiguity in the panel result. DIAGNOSIS

GT1042 / M85.16 (*CALR* exon 9)

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm when the small targeted NGS panel M85.1 (MPN multi-targeted NGS small variant panel) has failed, there is insufficient DNA to attempt this approach or there is ambiguity in the panel result. DIAGNOSIS

GT326 / M85.17 (*MPL* exon 10)

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm when the small targeted NGS panel M85.1 (MPN multi-targeted NGS small variant panel) has failed, there is insufficient DNA to attempt this approach or there si ambiguity in the panel result. DIAGNOSIS

GT649 / M85.11 (*BCR::ABL1* multiplex) *NB Please note chronic myeloid leukaemia has its own separate clinical indication (M84)*

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm where testing to date has not demonstrated a driver mutation OR the phenotype is such that there is reason to believe there is dual pathology. DIAGNOSIS

GT246 / M86.2 (high sensitivity *KIT* D816)

- For patients with a possible / suspected diagnosis of systemic mastocytosis. DIAGNOSIS

Small variant / copy number detection via panel

GT717 / M85.1 (MPN multi-target NGS limited panel small variant)

- For patients with a possible / suspected diagnosis of a myeloproliferative neoplasm. DIAGNOSIS

GT819 / M85.2 (Multi-target NGS panel)
GT736 / M85.36 (Multi-target NGS panel CNV)

- For patients with a known / suspected diagnosis of a myeloproliferative neoplasm where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm where demonstration of a specific genomic abnormality would allow access to a targeted treatment (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT
- For patients with a known diagnosis of a myeloproliferative neoplasm who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a myeloproliferative neoplasm receiving treatment where assessment of the disease response at a molecular level may influence treatment strategy (e.g. knowledge of molecular response prior to an allogeneic haematopoietic stem cell transplant). MONITORING DURING / POST-TREATMENT
- For patients with a known diagnosis of a myeloproliferative neoplasm who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Global copy number +/- structural variant via cytogenetics

GT1233 / M85.3 (Karyotype)
GT100 (SNP array)

- For patients with a suspected diagnosis of a myeloproliferative neoplasm where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a myeloproliferative neoplasm who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Targeted copy number +/- structural variant via FISH / RT-PCR

GT1211 / M85.5 (Other FISH)
GT763 / M85.24 (*BCR::ABL1* FISH)
GT152 / M85.31 (*ABL1* FISH)
GT699 / M85.7 (*FLIP1L1-PDGFRA* FISH)
GT373 / M85.25 (*PDGFRA* FISH)
GT1282 / M85.9 (*ETV6::PDGFRB* FISH)
GT1355 / M85.26 (*PDGFRB* FISH)
GT 147 / M85.27 (*FGFR1* FISH)
GT818 / M85.10 (*PCM1::JAK2* FISH)
GT13 / M85.28 (*JAK2* FISH)
GT172 / M85.29 (*MECOM* FISH)
GT1248 / M85.19 (Chr8 FISH)
GT198 / M85.20 (Chr7 FISH)
GT1224 / M85.21 (Chr5 FISH)
GT355 / M85.22 (Chr17 FISH)
GT614 / M85.12 (RT-PCR Other)

- For patients with a suspected diagnosis of a myeloproliferative neoplasm where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm who have undergone a change in their disease phenotype (e.g. increased blasts,

worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION

- For patients with a known diagnosis of a myeloproliferative neoplasm who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Structural variant detection via NGS panel

GT819 / M85.35 (Multi-target NGS panel – structural variant)

- For patients with a suspected diagnosis of a myeloproliferative neoplasm where demonstration of a clonal marker will assist in the diagnosis and WHO 2022 or ICC classification. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of a myeloproliferative neoplasm who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a myeloproliferative neoplasm who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Measurable residual disease testing

GT662 / M85.8 (MRD *FIP1L1::PDGFRA*)

- For patients with a known *FIP1L1::PDGFRA* fusion who are receiving disease modifying treatment where there is an expectation of a reduction in the clone size containing the *FIP1L1::PDGFRA* fusion and knowledge of this change will assist in decisions around ongoing / further management. MONITORING DURING TREATMENT

4. Test Package: Chronic Myeloid Leukaemia TP374

Chronic Myeloid Leukaemia Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT538 / M84.11 WGS Germline & Tumour - CML
GT1373 / M84.24 WGS Tumour First - CML
GT1357 / M84.25 WGS Follow-up Germline - CML

All paediatric and TYA patients with a confirmed or suspected diagnosis of a chronic myeloid leukaemia are eligible for whole genome sequencing (WGS), primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / (RELAPSE/REFRACTORY)

Tumour and germline samples can be submitted simultaneously (i.e M85.11) or separately i.e. tumour first (M84.24) followed by a germline when/if available (M84.25). At any presentation point either M84.11 or M84.24 +/- M84.25 is permissible, however once a non-contaminated germline has been submitted (either as part of M84.11 or M84.25) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

For adult patients with a confirmed or suspected diagnosis of chronic myeloid leukaemia, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Targeted tests

GT649 / M84.1 (*BCR::ABL1* multiplex)

- For patients with a possible / suspected diagnosis of chronic myeloid leukaemia. DIAGNOSIS

Small variant / copy number detection via panel

GT1426 Multi-target NGS panel
GT1414 Multi-target NGS panel CNV

- For patients with a known diagnosis of a chronic myeloid leukaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of chronic myeloid leukaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION

Global copy number +/- structural variant via cytogenetics

GT1096 / M84.4 Karyotype
GT1265 SNP array

- For patients with a suspected diagnosis of chronic myeloid leukaemia where demonstration of *BCR::ABL1* will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of a chronic myeloid leukaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of chronic myeloid leukaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a chronic myeloid leukaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Targeted copy number +/- structural variant via FISH / RT-PCR

GT1193 / M84.6 (FISH other)
GT1371 / M84.3 (*BCR::ABL1* FISH)
GT1034 / M84.12 (Chr8 FISH)
GT71 / M84.13 (Chr19 FISH)
GT73 / M84.14 (Chr7 FISH)
GT1424 / M84.15 (Chr5 FISH)
GT1345 / M84.16 (Chr17 FISH)

GT690 / M84.19 (*MECOM* FISH)
GT478 / M84.20 (*KMT2A* FISH)

- For patients with a suspected diagnosis of chronic myeloid leukaemia where demonstration of *BCR::ABL1* will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of a chronic myeloid leukaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of chronic myeloid leukaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a chronic myeloid leukaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Structural variant detection via NGS panel

GT99 / M84.22 (Multi-target NGS structural variant panel)

- For patients with a suspected diagnosis of chronic myeloid leukaemia where demonstration of *BCR::ABL1* will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of a chronic myeloid leukaemia to assist with prognostication which will inform patient management. DIAGNOSIS
- For patients with a known diagnosis of chronic myeloid leukaemia who have undergone a change in their disease phenotype (e.g. increased blasts, worsening cytopenias), where demonstration of clonal evolution may influence the treatment strategy. PROGRESSION
- For patients with a known diagnosis of a chronic myeloid leukaemia who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Drug Resistance Mutation testing

GT303 / M84.8 (*BCR::ABL1* TKD NGS)

- For patients with a known diagnosis of chronic myeloid leukaemia receiving a tyrosine kinase inhibitor who have failed to achieve an optimal response,

or have lost a previous response to treatment. The level of detection of this assay needs to be at least 5% (i.e. will detected variants within the *BCR::ABL1* TKD transcript with an allele frequency of at least 5%). PROGRESSION / RELAPSE / REFRACTORY

- In the event a variant is detected in *the BCR::ABL1* TKD, monitoring for the persistence of this variant is permissible. MONITORING

Measurable Residual Disease testing

GT31 / M84.2 (*BCR::ABL1* RT-qPCR p190 / p210)
GT673 / M84.23 (*BCR::ABL1* MRD rare)

- For patients with a known diagnosis of chronic myeloid leukaemia to monitor response to tyrosine kinase inhibitors. Frequency of monitoring should be as per ELN guidelines. DIAGNOSIS / PROGRESSION / RELAPSE / REFRACTORY / MONITORING

5. Test Package: Acute Lymphoblastic Leukaemia - B cell TP241

Acute Lymphoblastic Leukaemia – B cell Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT467 / M91.1 WGS Germline & Tumour - B-ALL
GT781 / M91.82 WGS Tumour First - B-ALL
GT1050 / M91.83 WGS Follow-up Germline - B-ALL

GT670 / M89.1 WGS Germline & Tumour – Acute Leukaemia Other
GT254 / M89.108 WGS Tumour First - Acute Leukaemia Other
GT825 / M89.109 WGS Follow-up Germline - Acute Leukaemia Other

All patients (of any age i.e. paediatric, TYA and adult) with an immunophenotypic diagnosis of acute lymphoblastic leukaemia (ALL) are eligible for WGS primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / (RELAPSE/REFRACTORY)

Tumour and germline samples can be submitted simultaneously (i.e. M91.1) or separately i.e. tumour first (M91.82) followed by a germline when/if available (M91.83). At any presentation point either M91.1 or M91.82 +/- M91.83 is permissible, however once a non-contaminated germline has been submitted (either as part of M91.1 or M91.83) this can be bioinformatically re-used as a germline for all subsequent tumour samples. Currently WGS is performed as an addition to any eligible to any standard of care.

Targeted tests

GT649 / M91.8 (BCR::ABL1 multiplex)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria which will have

prognostic implications and also direct treatment with a tyrosine kinase inhibitor. DIAGNOSIS

Small variant / copy number detection via panel

GT849 / M91.15 (NGS small variant panel – it is envisaged that the choice of gene footprint will ensure all relevant variants including putative resistance mutations are included).
GT350 / M91.78 (NGS Copy Number panel)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with a morphological diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Global copy number +/- structural variant via cytogenetics

GT1096 / M91.2 (Karyotype) Other diagnostic modalities such as a combination of SNP array and FISH testing can replace karyotyping providing required TATs are met.
GT295 (SNP array) SNP array is seen as a frontline test for ALL and can be performed in preference to karyotyping providing the required TATs are met. The SNP array should be at such a resolution such that it can detect small disruptive deletions (i.e. partial exon) in those genes deemed prognostic in the ALLTogether1 trial copy number abnormality (CNA) profile.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Targeted copy number +/- structural variant via FISH / RT-PCR

M91.4, M91.10, M91.24, M91.26, M91.44, M91.53-M91.62, M91.84-89 (Individual FISH tests)
Replaced by GT1052, GT1089, GT1163 / GT1180 / GT1191 / GT1300 / GT1308 / GT1309 / GT160 / GT200 / GT296 / GT301 / GT315 / GT483 / GT512 / GT546 / GT548 / GT56 / GT7 / GT723 / GT729 / GT756 / GT844 / GT85 / GT874
M91.6, M91.63 (Individual RT-PCR tests) non-quantitative
GT577 / GT739
It is expected that FISH / RT-PCR testing will not duplicate other structural / copy number variant testing unless required to meet rapid TATs.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL receiving/received treatment where assessment of disease response at a cytogenetic level may influence the subsequent treatment strategy. MONITORING DURING / POST-TREATMENT

Structural variant detection via NGS panel

GT329 / M91.7 (NGS Structural variant panel)

It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as SNP array, FISH, and (karyotype) if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification DIAGNOSIS / RELASPE/REFRACTORY

- For patients with an immunophenotypic diagnosis of ALL at diagnosis at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Drug Resistance Mutation testing

GT303 / M91.11 (BCR::ABL1 TKD variant testing)

- For patients with an immunophenotypic diagnosis of ALL known to have a BCR::ABL1 rearrangement whose response to a targeted inhibitor is such that there is clinical suspicion that there may be a resistance variant within the ABL1 tyrosine kinase domain. NB this assay should have a minimum variant allele frequency level of detection of 5%. MONITORING DURING TREATMENT

Measurable residual disease testing

GT31 / M91.9 (BCR::ABL1)
GT673 / M91.79 (Rare transcript BCR::ABL1 MRD)
GT214 / M91.14 (other MRD)
GT738 / M91.22 (Ig target identification for MRD)
GT1247 / M91.23 (Ig target quantification for MRD)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to identify Ig rearrangements suitable for use as measurable residual disease (MRD) targets (Ig target identification for MRD). DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL known to have the specific described genomic aberration of the assay, receiving/received curative treatment where assessment of disease response at a measurable residual disease [MRD] level may influence the subsequent treatment strategy. (Ig target quantification for MRD). MONITORING DURING / POST-TREATMENT

Pharmacogenomic targets

GT1185 / M91.80 (TPMT)
GT694 / M91.81 (NUDT15)

- For patients with an immunophenotypic diagnosis of ALL who are planned to receive a purine analogue as part of their treatment. DIAGNOSIS

6. Test Package: Acute Lymphoblastic Leukaemia - T cell TP34

Acute Lymphoblastic Leukaemia - T cell Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT183 / M91.1 WGS Germline & Tumour - T-ALL
GT687 / M91.82 WGS Tumour First - T-ALL
GT225 / M91.83 WGS Follow-up Germline - T-ALL

All patients (of any age i.e. paediatric, TYA and adult) with an immunophenotypic diagnosis of acute lymphoblastic leukaemia (ALL) are eligible for WGS at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS / RELASPE/REFRACTORY

Tumour and germline samples can be submitted simultaneously (i.e. M91.1) or separately i.e. tumour first (M91.82) followed by a germline when/if available (M91.83). At any presentation point either M91.1 or M91.82 +/- M91.83 is permissible, however once a non-contaminated germline has been submitted (either as part of M91.1 or M91.83) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an addition to any eligible to any standard of care.

Targeted tests

GT649 / M91.8 (BCR::ABL1 multiplex)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria which will have prognostic implications and also direct treatment with a tyrosine kinase inhibitor. DIAGNOSIS

Small variant / copy number detection via panel

GT849 / M91.15 (NGS small variant panel – it is envisaged that the choice of gene footprint will ensure all relevant variants including putative resistance mutations are included).
GT350 / M91.78 (NGS Copy Number panel)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with a morphological diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Global copy number +/- structural variant via cytogenetics

GT1096 / M91.2 (Karyotype) Other diagnostic modalities such as a combination of SNP array and FISH testing can replace karyotyping providing required TATs are met.
GT527 (SNP array) SNP array is seen as a frontline test for ALL and can be performed in preference to karyotyping providing the required TATs are met. The SNP array should be at such a resolution such that it can detect small disruptive deletions (i.e. partial exon) in those genes deemed prognostic in the ALLTogether1 trial copy number abnormality (CNA) profile.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Targeted copy number +/- structural variant via FISH / RT-PCR

M91.4, M91.10, M91.25, M91.39-M91.59, M91.61-62, M91.84, M91.88-M91.89 (Individual FISH tests)
Replaced by GT10, GT1089, GT1163, GT1180, GT1191, GT1300, GT1308, GT1309, GT200, GT239, GT296, GT301, GT512, GT844, GT85
M91.6 (Individual RT-PCR tests) non-quantitative

Replaced by GT739

It is expected that FISH / RT-PCR testing will not duplicate other structural / copy number variant testing unless required to meet rapid TATs.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications. DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL receiving/received treatment where assessment of disease response at a cytogenetic level may influence the subsequent treatment strategy. MONITORING DURING / POST-TREATMENT

Structural variant detection via NGS panel

GT329 / M91.7 (NGS Structural variant panel)

It is envisaged that NGS structural variant panels will most typically be used following other diagnostics such as SNP array, FISH, and (karyotype) if no likely driver genomic alteration has been identified. It is acknowledged that different laboratories may have slightly varying testing strategies which means this assay is deployed more frequently or earlier in the pathway. The limitations of a targeted RNA panel should be recognised such that deregulation of a proto-oncogene is unlikely to be detected by this methodology.

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to better refine the diagnosis as per WHO 2022 or ICC criteria. DIAGNOSIS
- For patients with immunophenotypic diagnosis of ALL at diagnosis / relapse/refractory presentation for prognostic implications including risk stratification DIAGNOSIS / RELASPE/REFRACTORY
- For patients with an immunophenotypic diagnosis of ALL at diagnosis at diagnosis / relapse/refractory to inform treatment (may include conventional chemotherapy regimens, non-chemotherapy regimens, or targeted inhibitors). DIAGNOSIS / RELASPE/REFRACTORY

Drug Resistance Mutation testing

GT303 / M91.11 (BCR::ABL1 TKD variant testing)

- For patients with an immunophenotypic diagnosis of ALL known to have a BCR::ABL1 rearrangement whose response to a targeted inhibitor is such that there is clinical suspicion that there may be a resistance variant within the ABL1 tyrosine kinase domain. NB this assay should have a minimum variant allele frequency level of detection of 5%. MONITORING DURING TREATMENT

Measurable residual disease testing

GT31 / M91.9 (BCR::ABL1)
GT673 / M91.79 (Rare transcript BCR::ABL1 MRD)
GT985 / M91.14 (other MRD)
GT332 / M91.22 (TCR target identification for MRD)
GT1149 / M91.23 (TCR target quantification for MRD)

- For patients with an immunophenotypic diagnosis of ALL at diagnosis to identify TCR rearrangements suitable for use as measurable residual disease (MRD) targets (TCR target identification for MRD). DIAGNOSIS
- For patients with an immunophenotypic diagnosis of ALL known to have the specific described genomic aberration of the assay, receiving/received curative treatment where assessment of disease response at a measurable residual disease [MRD] level may influence the subsequent treatment strategy. (TCR target quantification for MRD). MONITORING DURING / POST-TREATMENT

Pharmacogenomic targets

GT1185 / M91.80 (TPMT)
GT694 / M91.81 (NUDT15)

- For patients with an immunophenotypic diagnosis of ALL who are planned to receive a purine analogue as part of their treatment. DIAGNOSIS

7. Test Package: Chronic Lymphocytic Leukaemia TP533

Chronic Lymphocytic Leukaemia Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

For adult patients with a confirmed or suspected diagnosis of a chronic lymphocytic leukaemia, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Small variant / copy number detection via panel

GT1209 / M94.1 (Multi-target NGS panel small variant) [*TP53, BTK, PLCG2, BCL2*]
GT929 / M94.2 (Multi-target NGS panel copy number variant) [*TP53, ATM, DLEU2/7, RB1*, trisomy 12]

TP53 small variants and copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia who have not previously been identified to have disruption of the *TP53* gene who are about to embark on treatment. This testing should be repeated before each line of treatment providing no previous disruption of this gene has been identified. PRE-TREATMENT
BTK/PLCG2 small variants for patients with a known diagnosis of chronic lymphocytic leukaemia who have not responded to a BTK inhibitor or have lost a previous response to a BTK inhibitor where an alternative BTK inhibitor is being considered as part of treatment. PRIOR TO CHANGE IN TREATMENT
BCL2 small variants for patients with a known diagnosis of chronic lymphocytic leukaemia who have not responded to a BCL2 inhibitor or have lost a previous response to a BCL2inhibitor where an alternative BCL2 inhibitor is being considered as part of treatment. PRIOR TO CHANGE IN TREATMENT
ATM, DLEU2/7, RB1, trisomy 12 copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia, where the clinician has indicated knowledge of these copy number abnormalities will inform management of the patient. DIAGNOSIS

Global copy number +/- structural variant via cytogenetics

GT935 (SNP array for *TP53, ATM, DLEU2/7, RB1*, trisomy 12)

TP53 copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia who have not previously been identified to have disruption of the *TP53* gene who are about to embark on treatment. This

testing should be repeated before each line of treatment providing no previous disruption of this gene has been identified. PRE-TREATMENT *ATM, DLEU2/7, RB1,* trisomy 12 copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia, where the clinician has indicated knowledge of these copy number abnormalities will inform management of the patient. DIAGNOSIS

Targeted copy number +/- structural variant via FISH

GT923 / M94.4 *TP53* FISH
GT231 / M94.8 11q FISH
GT338 / M94.9 13q FISH
GT1281 / M94.10 chr12 FISH
GT926 Other FISH targets

TP53 copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia who have not previously been identified to have disruption of the *TP53* gene who are about to embark on treatment. This testing should be repeated before each line of treatment providing no previous disruption of this gene has been identified. PRE-TREATMENT *ATM, RB1,* trisomy 12 copy number variants for patients with a known diagnosis of chronic lymphocytic leukaemia, where the clinician has indicated knowledge of these copy number abnormalities will inform management of the patient. DIAGNOSIS

Structural variant detection

GT551 / M94.5 (IgHV somatic hypermutation multiplex sequencing)
GT1181 / M94.6 (IgHV somatic hypermutation NGS)

Patients with a known diagnosis of chronic lymphocytic leukaemia who are about to embark on their first-line of treatment. NB this only need to be undertaken once. PRE-TREATMENT

8. Test Package: Myeloma TP126

Myeloma (and other diseases with paraproteins) Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

For adult patients with a confirmed or suspected diagnosis of a plasma cell neoplasm, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Small variant / copy number detection via panel

GT429 / M92.1 (NGS small variant panel)
GT75 / M92.13 (NGS copy number variant panel)

Patients with a confirmed diagnosis of a plasma cell neoplasm where demonstration of high-risk genomic aberration(s) will alter patient management (may relate to intensity of chemotherapy, choice of single or tandem autologous HSCT, intensity and duration of maintenance, follow-up regimen) (17p deletion / 1p loss / 1q gain / chr5 gain / chr9 gain / chr 15 gain) DIAGNOSIS / PRE-TREATMENT (until a high-risk genomic aberration is demonstrated)

- Patients with a confirmed diagnosis of plasma cell myeloma where demonstration of a *BRAF, KRAS* or *NRAS* variant may allow access to a specific targeted inhibitor (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS / PRE-TREATMENT

Global copy number +/- structural variant via cytogenetics

GT178 (SNP array for TP53 / 1p / 1q / chr5 / chr9 / chr 15)
Patients with a confirmed diagnosis of a plasma cell neoplasm where demonstration of high-risk genomic aberration(s) will alter patient management (may relate to intensity of chemotherapy, choice of single or tandem autologous HSCT, intensity and duration of maintenance, follow-up regimen) (17p deletion / 1p loss / 1q gain / chr5 gain / chr9 gain / chr 15 gain) DIAGNOSIS / PRE-TREATMENT (until a high-risk genomic aberration is demonstrated)

Targeted copy number +/- structural variant via FISH

GT40 / M92.2 *IGH::FGFR3* FISH
GT890 / M92.3 *IGH::CCND3* FISH

GT187 / M92.4 *IGH::CCND1* FISH
GT549 / M92.5 *IGH::MAF* FISH
GT746 / M92.6 *IGH::MAFB* FISH
GT725 / M92.8 *IGH* FISH
GT1277 / M92.9 Hyperdiploidy copy number FISH
GT855 / M92.10 & M92.11 *CDKN2C* (del1p) & *CKSC1* (gain1q) FISH
GT383 / M92.12 *TP53* (del17p) FISH
GT632 / M92.14 *MYC* rearrangement FISH
GT565 Other FISH Targets

- Patients with a confirmed diagnosis of a plasma cell neoplasm where demonstration of high-risk genomic aberration(s) will alter patient management (may relate to intensity of chemotherapy, choice of single or tandem autologous HSCT, intensity and duration of maintenance, follow-up regimen) (*IGH::FGFR3, IGH::MAF, IGH::MAFB, CDKN2C* (del1p), *CKSC1* (gain1q), *TP53* (del17p), *MYC*). DIAGNOSIS / PRE-TREATMENT (until a high-risk genomic aberration is demonstrated)
- Patients with a confirmed diagnosis of plasma cell myeloma where demonstration of *IGH::CCND1* will allow access to venetoclax (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS / PRE-TREATMENT

Structural variant detection

GT1274 / M92.7 (NGS structural variant panel – delivered using DNA)

- Patients with a confirmed diagnosis of a plasma cell myeloma where demonstration of high-risk genomic aberration(s) will alter patient management (may relate to intensity of chemotherapy, choice of single or tandem autologous HSCT, intensity and duration of maintenance, follow-up regimen) (*IGH::FGFR3, IGH::MAF, IGH::MAFB, MYC*). DIAGNOSIS / PRE-TREATMENT (until a high-risk genomic aberration is demonstrated)
- Patients with a confirmed diagnosis of plasma cell myeloma where demonstration of *IGH::CCND1* will allow access to venetoclax (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS / PRE-TREATMENT

9. Test Package: Mature B Cell Neoplasms TP377

Mature B cell Neoplasms(excluding CLL) Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT1344 / M107.7 WGS Germline & Tumour - Marginal Zone Lymphoma
GT1389 / M107.9 WGS Tumour First - Marginal Zone Lymphoma
GT1365 / M107.10 WGS Follow-up Germline - Marginal Zone Lymphoma

GT1347 / M99.8 WGS Germline & Tumour - High Grade Lymphoma
GT1393 / M99.10 WGS Tumour First - High Grade Lymphoma
GT1351 / M99.11 WGS Follow-up Germline - High Grade Lymphoma

GT1350 / M96.7 WGS Germline & Tumour - Burkitt Lymphoma
GT1349 / M96.9 WGS Tumour First - Burkitt Lymphoma
GT1388 / M96.10 WGS Follow-up Germline - Burkitt Lymphoma

GT1356 / M93.3 & M95.7 WGS Germline & Tumour - Low Grade Lymphoma
GT1377 / M93.4 & M95.10 WGS Tumour First - Low Grade Lymphoma
GT1366 / M93.5 & M95.11 WGS Follow-up Germline - Low Grade Lymphoma

GT1378 / M101.4 & M182.3 WGS Germline & Tumour - ALK Positive Large B Cell Lymphoma
GT1360 / M101.6 & M182.5 WGS Tumour First - ALK Positive Large B Cell Lymphoma
GT1383 / M101.7 & M182.6 WGS Follow-up Germline - ALK Positive Large B Cell Lymphoma

GT1339 / M97.2 WGS Germline & Tumour - B Cell Lymphoma with 11q Aberration
GT1390 / M97.4 WGS Tumour First - B Cell Lymphoma with 11q Aberration
GT1363 / M97.5 WGS Follow-up Germline - B Cell Lymphoma with 11q Aberration

GT1341 / M98.2 WGS Germline & Tumour - B Cell Lymphoma with IRF4 Rearrangement
GT1392 / M98.4 WGS Tumour First - B Cell Lymphoma with IRF4 Rearrangement
GT1367 / M98.5 WGS Follow-up Germline - B Cell Lymphoma with IRF4 Rearrangement

GT1342 / M110.2 WGS Germline & Tumour - Follicular Lymphoma
GT1379 / M110.3 WGS Tumour First - Follicular Lymphoma

GT1343 / M110.4 WGS Follow-up Germline - Follicular Lymphoma

GT1381 / M100.4 WGS Germline & Tumour - Primary Mediastinal B Cell Lymphoma
GT1391 / M100.7 WGS Tumour First - Primary Mediastinal B Cell Lymphoma
GT1387 / M100.8 WGS Follow-up Germline - Primary Mediastinal B Cell Lymphoma

All paediatric and TYA patients with a confirmed or suspected diagnosis of a mature B cell neoplasm are eligible for WGS primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have
occurred. DIAGNOSIS/RELASPE/REFRACTORY

Tumour and germline samples can be submitted simultaneously (i.e M) or separately i.e. tumour first (M) followed by a germline when/if available (M). At any presentation point either M or M +/- M is permissible, however once a non-contaminated germline has been submitted (either as part of M or M) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

For adult patients with a confirmed or suspected diagnosis of a mature B cell neoplasm, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1)
or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Targeted tests

GT272 / M95.12, M104.2, M105.2 & M106.1 (*MYD88* L265P)
GT321 / M108.2 (*BRAF* V600)
GT1337 (*CD79B* Y196)
GT1253 / M95.1, M108.5, M109.1, M181.4 (*IgH*V somatic hypermutation testing multiplex seq)
GT1380 / M95.2, M108.6, M109.2, M181.5 (*IgH*V somatic hypermutation testing NGS)

- *MYD88* L265P: for patients with a suspected diagnosis of lymphoplasmacytic lymphoma OR large B cell lymphoma in an immune privileged (intra-ocular / CNS / testicular) where knowledge of the presence or absence of this variant will assist in diagnosis including that of IgM MGUS. DIAGNOSIS

- *MYD88* L265P: for patients with a diagnosis of a mature B cell neoplasm where knowledge of the presence or absence of this variant will assist in the treatment choice. PRE-TREATMENT
- *BRAF* V600: for patients with a suspected diagnosis of hairy cell leukaemia where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS
- *BRAF* V600: for patients whose clinical presentation would render them eligible for treatment with a BRAF-inhibitor in the event they had this variant (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT
- *CD79B* Y196: for patients with a suspected diagnosis of a large B cell lymphoma in an immune privileged (intra-ocular / CNS / testicular) where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS
- *IgH*V hypermutation testing: for patients with hairy cell leukaemia where knowledge of hypermutation will assist with management. DIAGNOSIS / PRE-TREATMENT

Small variant / copy number detection via panel (includes Resistance mutation testing)

It is envisaged that small variants and copy number variants will be delivered on a single panel.

GT267 / M93.6 (*BTK, PLCG2, RAS, MAP2K1, BCL2*), M95.4 (*EZH2*), M95.6 (*BTK2, PLCG2*), M102.5 (*TP53*), M103.4 (*CARD11, CREBBP, EZH2, ARID1A, EP300, MEF2B, FOXO1*), M104.1 (*MYD88, CXCR4*), M105.1 (*MYD88, CXCR4*), M108.1 (*BRAF*), M181.1 (*MAP2K1*), M110.1 (*MAP2K1*) (NGS small variant panel)
GT306 / M95.9 (*EZH2*) & M100.5 (*CD274/PDCD1LG2, REL*) (NGS copy number panel)

- *MYD88*: for patients with a suspected diagnosis of lymphoplasmacytic lymphoma OR large B cell lymphoma in an immune privileged (intra-ocular / CNS / testicular) where knowledge of the presence or absence of this variant will assist in diagnosis including that of IgM MGUS. DIAGNOSIS
- *CD79B*: for patients with a suspected diagnosis of a large B cell lymphoma in an immune privileged (intra-ocular / CNS / testicular) where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS
- *BRAF*: for patients with a suspected diagnosis of hairy cell leukaemia where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS
- *MAP2K1*: for patients with a suspected diagnosis of variant hairy cell leukaemia where knowledge of the presence or absence of this variant will assist in diagnosis.
- *CARD11, CREBBP, EZH2, ARID1A, EP300, MEF2B, FOXO1*: for patients with a known diagnosis of follicular lymphoma where knowledge

of the presence or absence of variants in these genes will assist with prognostication and treatment choice. DIAGNOSIS / PRE-TREATMENT

- *TP53*: for patients with a known diagnosis of mantle cell lymphoma where knowledge of the presence or absence of variants in these genes will assist with prognostication and treatment choice. DIAGNOSIS / PRE-TREATMENT
- *MYD88, CXCR4*: for patients with a diagnosis of a mature B cell neoplasm (predominantly lymphoplasmacytic lymphoma) where knowledge of the presence or absence of this variant will assist in the treatment choice. PRE-TREATMENT
- *BRAF*: for patients whose clinical presentation would render them eligible for treatment with a BRAF-inhibitor in the event they had an activating variant in this gene (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT
- *MAP2K1*: for patients whose clinical presentation would render them eligible for treatment with a MEK-inhibitor in the event they had an activating variant in this gene (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT
- *EZH2*: for patients whose clinical presentation would render them eligible for treatment with a EZH2-inhibitor in the event they had an activating variant in this gene (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT
- *BTK, PLCG2, RAS, MAP2K1, BCL2*: for patients whose clinical presentation would render them eligible for treatment with a specific inhibitor where knowledge of variants in one or more of these genes would assist in the treatment decision OR for patients already receiving a specific inhibitor who have not responded or are no longer responding as expected and where knowledge of variants in one or more of these genes may explain the lack of / loss of response (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT / RELAPSE / REFRACTORY
- *EZH2* deletion: for patients whose clinical presentation would render them eligible for treatment with a EZH2-inhibitor in the event they a deletion of this gene (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT
- *CD274/PDCD1LG2, REL* copy number abnormality: for patients with a suspected diagnosis of primary mediastinal large B cell lymphoma where knowledge of the presence or absence of these copy number abnormalities will assist with diagnosis. DIAGNOSIS

Global copy number +/- structural variant via cytogenetics

GT918 / M225.5 (karyotype)
GT444 / M97.1 (SNP array for 11q abnormalities)

- Karyotype: to be considered in exceptional circumstances where other testing has failed to assist with diagnosis. DIAGNOSIS
- SNP array for 11q abnormalities: for patients with a suspected diagnosis of a 'Burkitt-type' lymphoma in whom a *MYC* rearrangement has not been detected. DIAGNOSIS

Targeted copy number +/- structural variant via FISH / RT-PCR

GT852 / M95.3 (*IGH*) SV
GT414 / M95.5 (*EZH2*) CN
GT1394 / M96.1 & M99.1 (*MYC*) SV
GT576 / M96.2 & M99.2 (*IGH::MYC*)
GT664 / M96.3 & M99.3 (*IGK::MYC*)
GT312 / M96.4 & M99.4 (*IGL::MYC*)
GT613 / M96.5, M99.5 & M103.2 (*BCL2*) SV
GT646 / M99.6 & M103.1 (*IGH::BCL2*) SV
GT1285 / M96.6 / M99.7 / M103.3 (*BCL6*) SV
GT479 / M97.1 (11q) CN
GT369 / M98.1 (*IRF4*) SV
GT1404 / M100.1 & M100.2 (*CD274/PDCD1LG2*) SV & CN
GT1348 (*CIITA*) SV
GT534 / M100.3 (*REL*) CN
GT1354 / M101.1 (*ALK*) SV
GT1407 / M102.1 (*IGH::CCND1*) SV
GT868 / M102.2 (*CCND1*) SV
GT637 / M102.3 (*CCND2*) SV
GT1007 / M107.6 (*FOXP1*) SV
GT120 / M107.1, M107.3 & M107.4 (*MALT1*) SV
GT665 Other FISH Targets
GT779 / M107.2 & M107.5 (*BCL10*) SV

- *MYC / BCL2 / BCL6 / IGH / IGK / IGL*: for patients with a suspected diagnosis of a large B cell lymphoma OR Burkitt lymphoma where demonstration of the presence or absence of rearrangements of some of these genes will assist with diagnosis. It is recognised that labs will have specific algorithms as per which of these probes and in which order they are used in specific clinical / morphological / immunohistochemical scenarios. DIAGNOSIS
- *ALK* – for patients with a suspected diagnosis of a large B cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an *ALK*-rearrangement. DIAGNOSIS
- *IRF4* - for patients with a suspected diagnosis of a large B cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an IRF4-rearrangement. DIAGNOSIS
- 11q - for patients with a suspected diagnosis of a 'Burkitt-type' lymphoma in whom a MYC rearrangement has not been detected. DIAGNOSIS
- *CD274/PDCD1LG2, CIITA, REL* - for patients with a suspected diagnosis of a primary mediastinal B cell lymphoma where knowledge of

the presence or absence of these copy number abnormalities will assist with diagnosis. DIAGNOSIS

- *IGH::BCL2* – for patients with a suspected diagnosis of follicular lymphoma where demonstration of the presence or absence of this translocation will assist with diagnosis. DIAGNOSIS
- *BCL6* – for patients with a suspected diagnosis of follicular lymphoma who have not been shown to have an *IGH::BCL2* rearrangement where demonstration of the presence or absence of this translocation will assist with diagnosis. DIAGNOSIS
- *IGH::CCND1 / CCND1 / CCND2* – for patients with a suspected diagnosis of mantle cell lymphoma; it is envisaged that a rearrangement of *CCND1* will be sought first and only if not detected will *CCND2* be tested, if this also negative and the clinical suspicion for a diagnosis of mantle cell lymphoma remains high, the possibility to test for rearrangements of *CCND3* should be explored via WGS or custom panel. DIAGNOSIS
- *MALT1 / BCL10 / (BIRC3::MALT1 / IGH::BCL10 / IGH::MALT1) / FOXP1* - for patients with a suspected diagnosis of extra-nodal marginal lymphoma of mucosa-associated lymphoid tissue where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS
- *EZH2* - for patients whose clinical presentation would render them eligible for treatment with a EZH2-inhibitor in the event they had a deletion of this gene (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). PRE-TREATMENT

Structural variant detection via NGS panel

Given many clinically significant gene rearrangements in lymphoma involve the juxtaposition of the regulatory regions of highly expressed genes in B or T cells next to a gene relevant for cell proliferation or survival, there is often no resulting conventional 'fusion' protein (rather the rearrangement results in deregulation and over-expression). If no fusion protein results from a rearrangement, an RNA panel is unlikely to be useful in its detection, rather if an NGS panel approach is to be pursued this will likely require the use of DNA as the substrate.

GT795 NGS DNA based panel - structural variants
M95.8 (*IGH / IGK / IGL*)
M96.8 / M99.9 (*IGH / IGK / IGL / MYC / BCL2 / BCL6*)
M98.3 (*IRF4*)
M100.6 (*CD274 / CIITA*)
M102.4 (*IGH::CCDN1, CCND1, CCND2, CCND3*)
M103.5 (*IGH::BCL2, BCL2, BCL6*)
M107.8 (*IGH::MALT1, IGH::BCL10, FOXP1, BIRC3::MALT1*)
M101.5 (*CLTC::ALK, ALK::NPM1, ALK*)

GT50 NGS RNA based panel - structural variants
M100.6 (*CD274 / CIITA*)
M101.5 (*CLTC::ALK, ALK::NPM1, ALK*)

M107.8 (*BIRC3::MALT1*)

- *MYC / BCL2 / BCL6 / IGH / IGK / IGL*: for patients with a suspected diagnosis of a large B cell lymphoma OR Burkitt lymphoma where demonstration of the presence or absence of rearrangements of some of these genes will assist with diagnosis. It is recognised that labs will have specific algorithms as per which of these probes and in which order they are used in specific clinical / morphological / immunohistochemical scenarios. DIAGNOSIS
- *ALK* – for patients with a suspected diagnosis of a large B cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an ALK-rearrangement. DIAGNOSIS
- *IRF4* - for patients with a suspected diagnosis of a large B cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an IRF4-rearrangement. DIAGNOSIS
- *CD274/PDCD1LG2, CIITA* - for patients with a suspected diagnosis of a primary mediastinal B cell lymphoma where knowledge of the presence or absence of these copy number abnormalities will assist with diagnosis. DIAGNOSIS
- *IGH::BCL2* – for patients with a suspected diagnosis of follicular lymphoma where demonstration of the presence or absence of this translocation will assist with diagnosis. DIAGNOSIS
- *BCL6* – for patients with a suspected diagnosis of follicular lymphoma who have not been shown to have an *IGH::BCL2* rearrangement where demonstration of the presence or absence of this translocation will assist with diagnosis. DIAGNOSIS
- *IGH::CCND1 / CCND1 / CCND2* – for patients with a suspected diagnosis of mantle cell lymphoma; it is envisaged that a rearrangement of *CCND1* will be sought first and only if not detected will *CCND2* be tested, if this also negative and the clinical suspicion for a diagnosis of mantle cell lymphoma remains high, the possibility to test for rearrangements of *CCND3* should be explored via WGS or custom panel. DIAGNOSIS
- *MALT1 / BCL10 / (BIRC3::MALT1 / IGH::BCL10 / IGH::MALT1) / FOXP1* - for patients with a suspected diagnosis of extra-nodal marginal lymphoma of mucosa-associated lymphoid tissue where knowledge of the presence or absence of this variant will assist in diagnosis. DIAGNOSIS

10. Test Package: Mature T Cell Neoplasms TP58

Mature T cell and NK cell Neoplasms Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT1352 / M116.3 WGS Germline & Tumour - Hepatosplenic T Cell Lymphoma
GT1361 / M116.5 WGS Tumour First - Hepatosplenic T Cell Lymphoma
GT1364 / M116.6 WGS Follow-up Germline - Hepatosplenic T Cell Lymphoma

GT1386 / M111.5 WGS Germline & Tumour - T Cell NHL
GT1358 / M111.7 WGS Tumour First - T Cell NHL
GT1353 / M111.8 WGS Follow-up Germline - T Cell NHL

GT1369 / M112.5 WGS Germline & Tumour - ALK Negative Anaplastic Large Cell Lymphoma
GT1362 / M112.7 WGS Tumour First - ALK Negative Anaplastic Large Cell Lymphoma
GT1359 / M112.8 WGS Follow-up Germline - ALK Negative Anaplastic Large Cell Lymphoma

GT1376 / M115.2 WGS Germline & Tumour - NK Cell/Gamma-Delta T Cell Lymphoma
GT1384 / M115.3 WGS Tumour First - NK Cell/Gamma-Delta T Cell Lymphoma
GT1372 / M115.4 WGS Follow-up Germline - NK Cell/Gamma-Delta T Cell Lymphoma

All paediatric and TYA patients with a confirmed or suspected diagnosis of a mature T or NK cell neoplasm are eligible for WGS primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS/RELASPE/REFRACTORY

Tumour and germline samples can be submitted simultaneously (i.e M) or separately i.e. tumour first (M) followed by a germline when/if available (M). At any presentation point either M or M +/- M is permissible, however once a non-contaminated germline has been submitted (either as part of M or M) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an **addition** to any standard of care testing that an individual is eligible for.

For adult patients with a confirmed or suspected diagnosis of a mature B cell neoplasm, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Small variant detection via panel

GT1279 / M111.1 (*RHOA, DNMT3A, IDH2, TET2, PLCG1, CARD11, IRF4, POT1, VAV1, FYN*), M114.1, M115.1 & M116.1 (*STAT3, STAT5b*)

- *RHOA, DNMT3A, IDH2, TET2, PLCG1, CARD11, IRF4, POT1, VAV1, FYN* – for patients with a suspected diagnosis of a mature T cell neoplasm where knowledge of the presence or absence of variants in these genes will assist in the differentiation from reactive looking T cells. DIAGNOSIS
- *STAT3, STAT5b* – for patients with a suspected diagnosis of T-cell large granular lymphocyte leukaemia, NK-cell large granular lymphocyte leukaemia or hepatosplenic T cell lymphoma where knowledge of the presence or absence of variants in these genes will assist with diagnosis. DIAGNOSIS

Global copy number +/- structural variant via cytogenetics

GT918 / M225.5 (karyotype)

- Karyotype: to be considered in exceptional circumstances where other testing has failed to assist with diagnosis. DIAGNOSIS

Targeted copy number +/- structural variant via FISH / RT-PCR

GT1146 / M111.4 (*TRA, TRB, TRG*)
GT256 / M112.3 (*IRF4/DUSP22*)
GT733 / M112.4 (*TP63*)
GT1385 / M182.1 (*ALK::NPM1*)
GT1416 / M182.2 (*ALK*)
GT59 / M113.1 (*TCL1A*)
GT1422 / M113.2 (chromosome 8)
GT345 / M116.2 (chromosome 7)
GT1338 Other FISH Targets

- *TRA, TRB, TRG* - for patients with a suspected diagnosis of a mature T cell neoplasm where knowledge of the presence or absence of rearrangements of these genes will assist in the differentiation from reactive looking T cells. DIAGNOSIS

- *IRF4/DUSP22, TP63* – for patients with a known diagnosis of *ALK*-negative anaplastic large cell lymphoma where knowledge of the presence or absence of rearrangements of these genes will assist in prognostication and treatment decisions. DIAGNOSIS, PRE-TREATMENT
- *ALK, ALK::NPM1* - for patients with a suspected diagnosis of *ALK*-positive anaplastic large cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an *ALK* rearrangement. DIAGNOSIS
- *TCL1A* – for patients with a suspected diagnosis of T-cell prolymphocytic leukaemia where knowledge of the presence or absence of a rearrangement of this gene will assist with diagnosis. DIAGNOSIS
- Trisomy 8 – for patients with a suspected diagnosis of T-cell prolymphocytic leukaemia where knowledge of the presence or absence of this copy number abnormality will assist with diagnosis. DIAGNOSIS
- Iso7q – for patients with a suspected diagnosis of hepatosplenic T cell lymphoma where knowledge of the presence or absence of this copy number abnormality will assist with diagnosis. DIAGNOSIS

Structural variant detection via NGS panel

GT821 NGS DNA based panel - structural variants
M111.6 (*TRA, TRB, TRG*)
M112.6 (*IRF4/DUSP22, TP63*)
M113.3 (*TCL1A*)

GT1153 NGS RNA based panel - structural variants
M112.6 (*TP63*)
M182.4 (*ALK::NPM1, ALK*)

- *TRA, TRB, TRG* - for patients with a suspected diagnosis of a mature T cell neoplasm where knowledge of the presence or absence of rearrangements of these genes will assist in the differentiation from reactive looking T cells. DIAGNOSIS
- *IRF4/DUSP22, TP63* – for patients with a known diagnosis of *ALK*-negative anaplastic large cell lymphoma where knowledge of the presence or absence of rearrangements of these genes will assist in prognostication and treatment decisions. DIAGNOSIS, PRE-TREATMENT
- *ALK, ALK::NPM1* - for patients with a suspected diagnosis of *ALK*-positive anaplastic large cell lymphoma whose immunohistochemistry is such that there is suspicion they may have an *ALK* rearrangement. DIAGNOSIS
- *TCL1A* – for patients with a suspected diagnosis of T-cell prolymphocytic leukaemia where knowledge of the presence or absence of a rearrangement of this gene will assist with diagnosis.
- Trisomy 8 – for patients with a suspected diagnosis of T-cell prolymphocytic leukaemia where knowledge of the presence or absence of this copy number abnormality will assist with diagnosis. DIAGNOSIS

- iso7q – for patients with a suspected diagnosis of hepatosplenic T cell lymphoma where knowledge of the presence or absence of this copy number abnormality will assist with diagnosis. DIAGNOSIS

11. Test Package: Histiocytosis TP182

Histiocytosis Testing Criteria

The following testing criteria describe the genomic tests that may be used during the analysis of a patient's samples to refine diagnosis, prognosis and treatment decisions. Not all tests are necessary for every patient and will be selected on the basis of the patient's clinical presentation.

WGS tests

GT593 / M117.16 WGS Germline & Tumour - Histiocytosis
GT35 / M117.17 WGS Tumour First - Histiocytosis
GT836 / M117.18 WGS Follow-up Germline - Histiocytosis

All paediatric and TYA patients with a confirmed or suspected diagnosis of histiocytosis are eligible for WGS primarily at diagnosis. If WGS has not occurred at diagnosis, undertaking this test at relapse or if refractory to a line of treatment may be appropriate. In exceptional circumstances, repeat WGS may be indicated if there is a high probability that significant clonal evolution is likely to have occurred. DIAGNOSIS/RELASPE/REFRACTORY

Tumour and germline samples can be submitted simultaneously (i.e M117.16) or separately i.e. tumour first (M117.17) followed by a germline when/if available (M117.18). At any presentation point either M117.16 or M117.17 +/- M117.18 is permissible, however once a non-contaminated germline has been submitted (either as part of M117.16 or M117.18) this can be bioinformatically re-used as a germline for all subsequent tumour samples.

Currently WGS is performed as an addition to any eligible to any standard of care.

For adult patients with a confirmed or suspected diagnosis of histiocytosis, WGS is available under the indication M235 i.e. Exhausted standard of care testing and or treatment, providing they meet this eligibility criteria. Samples can be submitted simultaneously (M235.1) or separately i.e. tumour first (M235.2) followed by a germline when/if available (M235.3).

Targeted tests

GT69 / M117.19 High sensitivity *BRAF* V600E

- For patients with a suspected diagnosis of histiocytosis where demonstration of the *BRAF* p.(V600E) variant will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of histiocytosis where demonstration of a specific genomic abnormality would allow access to a

targeted treatment (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT

- For patients with a known diagnosis of histiocytosis receiving treatment where assessment of the disease response at a molecular level may influence treatment strategy (e.g. knowledge of molecular response prior to an allogeneic haematopoietic stem cell transplant). MONITORING DURING / POST-TREATMENT
- For patients with a known diagnosis of histiocytosis who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT
-

Small variant via panel

GT892 / M117.1 (NGS small variant panel)

- For patients with a suspected diagnosis of histiocytosis where demonstration of a clonal marker will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of histiocytosis where demonstration of a specific genomic abnormality would allow access to a targeted treatment (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT
- For patients with a known diagnosis of histiocytosis receiving treatment where assessment of the disease response at a molecular level may influence treatment strategy (e.g. knowledge of molecular response prior to an allogeneic haematopoietic stem cell transplant). MONITORING DURING / POST-TREATMENT
- For patients with a known diagnosis of histiocytosis who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of mutations post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Targeted structural variant via FISH

GT579 / M117.3 (*ALK* rearrangement FISH)
GT426 / M117.7 (*BRAF* rearrangement FISH)
GT456 / M117.12 (*NTRK1* rearrangement FISH)

- For patients with a suspected diagnosis of histiocytosis where demonstration of a clonal marker will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of histiocytosis where demonstration of a specific genomic abnormality would allow access to a targeted treatment (NB there should be an expectation that

the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT

- For patients with a known diagnosis of histiocytosis receiving treatment where assessment of the disease response at a molecular level may influence treatment strategy (e.g. knowledge of molecular response prior to an allogeneic haematopoietic stem cell transplant). MONITORING DURING / POST-TREATMENT
- For patients with a known diagnosis of histiocytosis who have received curative intent treatment (i.e. allogeneic haematopoietic stem cell transplant [HSCT]) to monitor for presence of genomic abnormalities post-HSCT, particularly in the context of <100% donor chimerism in order to inform donor lymphocyte infusion strategy. MONITORING POST-TRANSPLANT

Structural variant detection via NGS panel

GT914 / M117.2 (Multi-target NGS panel – structural variant)

- For patients with a suspected diagnosis of histiocytosis where demonstration of a clonal marker will assist in the diagnosis. DIAGNOSIS
- For patients with a known diagnosis of histiocytosis where demonstration of a specific genomic abnormality would allow access to a targeted treatment (NB there should be an expectation that the genomically-determined treatment will be available in response to the demonstration (or not) of a specific abnormality). DIAGNOSIS, PRE-TREATMENT, PRIOR TO CHANGE IN TREATMENT

12. Test Package: Chimerism Testing TP401

Chimerism Testing

GT1368 / M118.1 STR Chimerism testing post-allogeneic haematopoietic stem cell transplant

- Individuals who have undergone an allogeneic haematopoietic stem cell transplant where determination of the level of engraftment i.e. chimerism of the bone marrow / peripheral blood, would be informative in patient management. In the absence of nationally agreed guidelines, specific cell lineage(s), sample type and timing of testing should follow locally agreed protocols. INITIAL TESTING OF HOST & DONOR PRE-TRANSPLANT / MONITORING

GT1370 / M118.2 XY chromosome FISH post-allogeneic haematopoietic stem cell transplant

- Individuals who have undergone a sex-mismatched allogeneic haematopoietic stem cell transplant where determination of the level of engraftment i.e. chimerism of the bone marrow / peripheral blood, would be informative in patient management. In the absence of nationally agreed guidelines, specific cell lineage(s), sample type and timing of testing should follow locally agreed protocols. MONITORING

GT1335 / M242.1 STR Chimerism testing post-allogeneic solid organ transplant

- Individuals who have undergone an allogeneic solid organ transplant where there is a clinical concern that there may be passenger lymphocyte syndrome i.e. evidence of lymphocytes from the donor in the host. It should be noted that this testing is not implemented routinely but rather on request from the treating clinicians. INITIAL TESTING OF HOST & DONOR PRE-TRANSPLANT (accepting that there is often not a suitable donor sample for comparative testing)/ MONITORING

GT1336 / M242.2 XY chromosome FISH post-allogeneic solid organ transplant

- Individuals who have undergone a sex-mismatched allogeneic solid organ transplant where there is a clinical concern that there may be passenger lymphocyte syndrome i.e. evidence of lymphocytes from the donor in the host. It should be noted that this testing is not implemented routinely but rather on request from the treating clinicians. MONITORING

13. Test Package: Clonality Testing TP62

Clonality Testing

GT1423 / M225.1 B-cell clonality testing multiplex sequencing
GT1408 / M225.2 B-cell clonality testing NGS

- Individuals where there is a suspicion of a clonal B cell malignancy or where otherwise demonstrating the presence or absence of clonal B cells will aid in patient management. DIAGNOSIS

GT39 / M225.3 & M111.2 T-cell clonality testing multiplex sequencing
GT508 / M225.4 & M111.3 T-cell clonality testing NGS

- Individuals where there is a suspicion of a clonal T cell malignancy or where otherwise demonstrating the presence or absence of clonal T cells will aid in patient management. DIAGNOSIS

There are certain clinical presentations e.g. T cell rich B cell lymphoma where undertaking both B and T clonality is appropriate.

14. Test Package: HaemOnc Tumours - Exhausted SOC TP245

Proven or suspected haematological tumour exhausted all standard of care testing and treatment.

GT104 / M235.1 WGS Germline & Tumour - exhausted SOC
GT88 / M235.2 WGS Tumour First - exhausted SOC
GT1076 / M235.3 WGS Follow-up Germline - exhausted SOC

- All patients of any age who do not have another WGS option in the test directory who have a proven or suspected haematological tumour and have exhausted all standard of care testing and treatment are in theory eligible under this category. However, there should be a specific question that it is hoped WGS will answer and a realistic prospect that the data currently returned as part of a standard analysis could do this. Patients who are potentially eligible under this criteria should be discussed with the relevant GLH haematological malignancies medical lead or their designee in order to seek their agreement that WGS is an appropriate testing choice based on the clinical question. All patients sequenced under this indication should have data collected post-analysis as to whether the testing had an impact on patient care. DIAGNOSIS / RELAPSE/REFRACTORY