The Belgian next generation sequencing guidelines for haematological and solid tumours

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1. DEFINITIONS

Accreditation: procedure by which an authoritative body gives formal recognition that an organization is competent to carry out specific tasks.[1]

Allelic read percentage or allelic frequency: is the percentage of variant reads in a background of normal reads.

Analytical accuracy: measurement of the discrepancy between the measured value and the true value. Can be established by analysing well-characterised reference samples with known confirmed sequence variants.[2-4]

Analytical sensitivity: likelihood that the assay will detect the targeted sequence variations if present (true positive rate).[5]

Analytical specificity: probability that the assay will not detect a sequence variation when none are present (true negative rate).[5]

cDNA: copy DNA

Library: collection of DNA fragments.

FASTQ format: is a text-based format for storing nucleotide sequence and its corresponding quality scores (encoded with a single ASCII character).

Fusion gene: A gene resulting from joining parts of two different genes. A cancer-related fusion gene produces an activated or altered function of the fusion partner, which contributes to the cancer phenotype.

Limit of detection: is the lowest actual percentage of variants that can be consistently detected.

Log file: is a file that records events that occur in an operating system or other software runs, or messages between different users of communication software.

Pipeline: is a bioinformatics workflow management system which executes a series of computational or data manipulation steps that relate to bioinformatics and is organized so that the output of one is the input of the following.

Precision: degree of agreement between replicate measurements of the same material that can be determined by assessing the reproducibility (between-run precision, the consistency of results from the same sample under different conditions) and repeatability (within-run precision, the consistency of results from the same sample under the same condition).[5]

Referral laboratory: 'external laboratory to which a sample is submitted for examination'.[1]

Reference Materials: are well-characterised, homogeneous, stable samples with certified properties for their intended purpose.[6]

Reportable range: region of the genome for which the sequence derived by the NGS test meets the quality determined during the validation process.[5]

Region of interest (ROI): region of the genome that the NGS test claims to assess.

Supporting fusion reads: RNA-derived sequencing reads that span a gene fusion or exon skipping event.

Targeted NGS: the sequencing of a subset of genes or regions of the genome.

Template: is the RNA or DNA strand that serves as a pattern for the generation of cDNA or another DNA molecule, respectively.

Turnaround time: 'elapsed time between two specified points through pre-examination, examination and post-examination processes'.[1]

Validation: 'confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled'.[1]

Variant: a called nucleotide that differs from the reference sequence. Verification: 'confirmation, through provision of objective evidence, that specified requirements have been fulfilled'.[1]

4.2. INTRODUCTION

Targeted next generation sequencing (NGS) analysis is a complex procedure including two main parts, the 'wet bench' part or lab experimental test and the 'dry bench' or bioinformatics part. Both parts are composed of many steps and for each of these steps optimal assay conditions and analysis settings must be determined.[7]

The aim of this document is to provide guidelines to facilitate and harmonise implementation, verification and validation of targeted NGS tests to detect acquired somatic mutations in DNA (or RNA), or acquired fusion genes in RNA, in (haemato)-oncology. These guidelines aim to harmonise clinical conclusions if a sample is processed through different pipelines by different operators at different times and at different sites.[8] Actual platforms are based on different chemistries and each of them has specific parameters and test requirements. These guidelines aim to provide generic recommendations to all stakeholders (laboratories, BELAC-auditors, experts, etc.) valid independently of the platform used. They are to be considered as complementary to the International Organization for Standardization (ISO)15189 standard (medical laboratories) as well as to other inter- national NGS guidelines, for example those from EuroGentest, the Association for Clinical Genetic Science (ACGS), the Dutch Society for Clinical Genetic Laboratory Diagnostics (VKGL), the College of American Pathologists (CAP), IQN Path ASBL and the Centers for Disease Control and Prevention (CDC).[3,5,7-10]

Validation or verification, and internal quality control (IQC) procedures at the different steps in the workflow (by defining quality parameters and by measuring quality metrics) and on the whole process (by determining performance characteristics), must be performed to assure and maintain accurate test results. Moreover, periodic external quality assessment (EQA) should be performed in order to ensure that performance complies with (inter)nationally accepted performance criteria.

a. GENERAL REQUIREMENTS FOR TARGETED NGS TESTS TRACEABILITY

4.3.1 General documentation

Laboratories should have Standard Operating Procedures (SOPs) for all steps involved in sample preparation, wet and dry bench parts of the NGS process, as well as in the review and reporting of results according to the requirements of ISO 15189.[2,4,8] Accurate systems for tracking the software version used should be available.

4.3.2 Logistical documentation

As required by the ISO 15189 standard, for each test, information regarding the operation of instruments (e.g. calibration and maintenance records, log files, etc.) as well as any essential information on critical reagents (e.g. lot number, expiration data, etc.) should be recorded.

4.3.3 Targeted gene panel description documentation

During the test development, a precise description (at the genome and transcript level) of all specific gene hotspots that can be analysed should be available. The minimally required variants to be analysed for a specific tumour type are those which have a proven clinical utility (to define diagnosis and/or to predict response or resistance to specific cancer therapies (therapeutic) and/or to determine prognosis (patient outcome) for that specific tumour type. These variants have been established within the expert group of the 'Commission of Personalized Medicine' (ComPerMed). In addition, the NGS gene panel may also contain a limited number of gene targets with hotspots that are expected to have clinical relevance in the future, in a specific or in another tumour type. All variants which are part of the validation should be listed with the transcript accession (NM-reference) number of the gene, all exons and the specific, delineated regions that are targeted. Targeted NGS gene panels on DNA level should contain single nucleotide variants (SNVs) and small indels (Insertion and/or Deletion of few bases) but other types of alterations (large indels and amplifications) can also be included or might be detected by other techniques.[8] The size up to which indels can be detected should be carefully determined and reported in the validation dossier. If alterations other than SNVs and small indels are included, a thorough validation and quality assurance should be established for each type of these reported molecular alterations. At the RNA level, next to SNVs and indels, clinically

important gene fusions and exon skipping events should be detected with sufficient sensitivity as demonstrated in the validation report.

4.3.4 Validation/verification report

The experimental approach, results, conclusions and any other relevant details of the validation or verification process (validation and verification chapters) should be recorded in a validation/verification report. The validation report should contain the empirically determined performance characteristics of the test (e.g. sensitivity, specificity, precision, accuracy and limit of detection) as well as critically relevant quality metrics (test development and validation chapters). The validation/verification criteria can be reported in peer-reviewed publications.[11] Any deviation from the developed and validated test should be recorded and documented according to ISO 15189 standards and revalidation/reverification (validation chapter) should be considered.[2,3,5,12]

4.3.5 Test run documentation

For each run, a test report should contain the values of relevant quality metrics in order to demonstrate that the reported sequence meets the quality criteria set in the validation report. A test report should also contain the sequences which are in the reportable ranges.

4.3.6 Data storage

Storage of NGS data should be according to the guidelines of the laboratory, which are present in the laboratory guide. However, it is required that the FASTQ and/or Bam files are stored for at least 1 year and the Vcf and Bed files for at least 4 years.[7,9,14]

4.3.7 Data transfer

All data transfers should use secure network connections that allow verification of the data transfers. An external hard disk between the various components of the computing hardware i.e. from sequencer to the analytical computer and/or to storage location can also be used.[2] The policy and procedure should be adequately documented.

Appropriate and validated measures should be taken to avoid data corruption during transfer (e.g. by using checksum generation during file transfer, management of data permissions, secured backup of copies of FASTQ files maintained elsewhere).[2] Appropriate error messages should be generated where case corrupted files are detected.

4.3.8 Reference material

Reference materials can exist or variant-engineered human cell lines (Reference sample) as well as informatics data files (Reference informatics data file). Reference materials should be used for test validation/verification prior to implementation and for continued quality assessment of the validated NGS pipeline (validation, verification and quality control chapters).[5]

Reference samples should have well-documented sequencing data, should ideally be available on a continuous basis and should resemble as much as possible the patient specimens in order to accurately reflect the testing conditions.[2,5,12]

Reference informatics data files are files created by computational methods simulating patient sample sequences or by sequencing biological samples with well-documented variants (SNVs and indels for DNA or RNA, and gene fusions and exon skipping for RNA) and allelic frequency close to real data.[2,5,12] They should be compatible with the sequencing platform's output taking into account the used platform characteristics such as read length, read number, etc. These reference informatics data files can be used for the validation of the dry bench part.[5]

A combination of reference informatics data files and reference samples is recommended to provide a robust

framework for test validation/verification (validation, verification and quality control chapters).[5]

4.3.9 Risk analysis

The ISO 15189 standard requires that the laboratory has a documented plan how to evaluate the impact of work processes and potential failures on examination results as they affect patient safety, and that the laboratory modify processes to reduce or eliminate the identified risks, and document decisions and actions taken.[1] As NGS workflows are complex and consist of many different steps (from pre-analytical step to tertiary interpretation), risk analysis is particularly appropriate to reduce potential erroneous results and should be performed prior to implementation, e.g. as part of the validation process. Any identified risk should be included in the validation report (e.g. in a Fishbone diagram), and addressed appropriately within the validation of the test.

4.3.10 Outsourcing

If tests are outsourced, the ISO 15189 requires that the referring laboratory has a procedure for the selection and evaluation of the referral laboratory. The referral laboratory should be accredited according to ISO 15189 for the NGS test in (haemato)-oncology and licensed by the Minister of Public Health. In addition, the quality of the referral laboratory should be continuously monitored by the referring laboratory. Responsibilities towards the interpretation and reporting of the results stay with the referring laboratory.[1]

Specifically for NGS tests, there is a tendency to outsource only parts of the tests that may not necessarily comply with present license requirements. In any case, however, in agreement with the ISO 15189 standard, for any outsourced parts of the activity, the referring laboratory should be able to monitor the quality of the subcontractor, and demonstrate that outsourcing does not negatively influence the reliability of the final results. The outsourcing of parts of the NGS pipeline should be subject to the required risk analysis.

4.4. TECHNICAL REQUIREMENTS AND PERFORMANCE SPECIFICATION

It is necessary to prove that the test performs to the highest achievable level of performance required for answering to a particular clinical question and that this level of performance is maintained in all routine analyses.[11] Desired performance characteristics for performing any NGS in (haemato)-oncology should be defined in advance and integrated in the validation plan.

The level of validation/verification depends on the availability of acceptable performance specifications (*Figure 1*):

- in case of a new in-house or modified IVD CE-marked test or technology, the entire process should be validated (validation chapter) for meeting the a priori defined performance specifications.
- in case of the implementation of a IVD-CE marked test or technology with documented performance specifications or of a validated test with minor modification of the experimental protocol or of the composition of the gene panel (e.g. when adding a new gene), only a verification (verification chapter) is required.

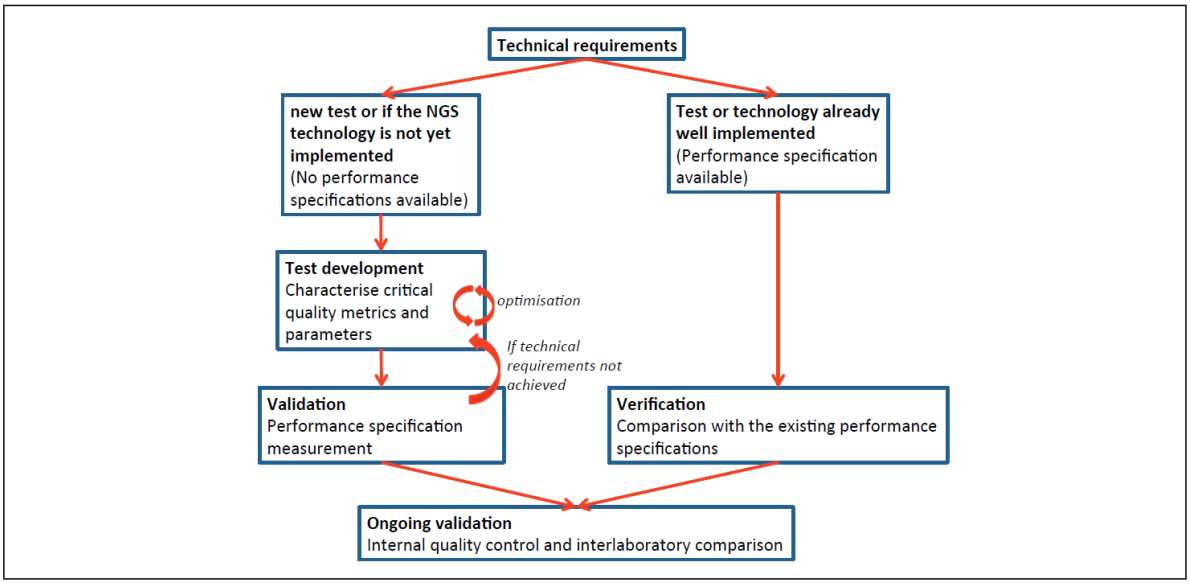


FIGURE 1 Workflow for the implementation of a NGS test.

4.5. SAMPLE ACCEPTANCE CRITERIA AND SAMPLE PREPARATION

4.5.1 Sampling and fixation

Sample preparation is a crucial step for all high-quality molecular analyses. Samples of poor quality (e.g. due to fixation artefacts) or with insufficient RNA or DNA quantity can significantly affect the sensitivity and specificity of the test (validation chapter) and can lead to false negative or false positive results.[2]

For tumour tissue, the fixation of sample after surgical removal should be validated for the purpose of NGS sequence analysis. It is recommended to proceed to the fixation within 1h after (surgical) removal preferably in 10% neutral buffered formalin during a specific timelapse (generally between 6-72h). Delayed or suboptimal fixation may result in RNA or DNA degradation due to apoptosis and/or necrosis.[15] For blood and bone marrow samples, recipients with common anticoagulants such as EDTA should be used and samples should be processed in time, preferably within 24 hours, to assure RNA and DNA integrity.[16] NGS on decalcified bone samples is possible if a weak acid- or EDTA-based decalcification protocol has been properly administered, though it may affect the success rate of the NGS test.[17,18]

4.5.2 Specimen selection quality

The sample (tissue from primary tumour or metastasis, blood, bone marrow, etc.) should contain sufficient neoplastic cells. The minimally required percentage of neoplastic cells in a background of normal cells, if applicable, should be defined during the validation process, taking into account that the assessment of the tumour cell content by different pathologists can be imprecise and inaccurate.[19] The latter will be estimated on Haematoxylin and Eosin (HE) stained adjacent slides for biopsies and by cytological and/or flow cytometric examination for blood/bone marrow by adequately trained staff with documented competence. For formalin fixed paraffin embedded (FFPE) material, macrodissection or (manual) micro- dissection may be performed to enrich the neoplastic cell proportion.[1,7] The estimated neoplastic cell content of the material used for NGS analysis should be reported and taken into account in the technical validation of the (negative) results.

In case neoplastic cell content is below the minimally required percentage as determined in the validation report, or can not be exactly determined e.g. in body fluid, laboratories should state in the clinical report that

negative results (e.g. the absence of any mutation) may not be reliable and that repeated analysis on material with a sufficiently high neoplastic cell content is advised. The treating physician should receive this information as soon as possible in order to allow for repeated sampling with as little delay as possible. A registration of transfer/receipt of this information should be kept.

4.5.3 DNA/RNA quality and quantity

After DNA/RNA extraction, DNA quality (e.g. purity, degradation) and/or quantity can be assessed by fluorescence, by optical density or by qPCR amplification. The laboratories should determine a measurement method for DNA/RNA quality and/or quantity and should evaluate how DNA/RNA quantity and/or quality influence the reliability of the results during the validation process (validation chapter). The minimal amount of specimen required and the success rate of the pipeline considering the DNA/RNA quantity/quality of the representative clinical samples should be evaluated during the validation process.

4.6. TEST DEVELOPMENT

4.6.1 General

For each NGS test or technology not yet implemented, usually no performance specifications are available and a protocol (SOP) should be established. Desired performance characteristics should be adequately defined in advance and integrated in the development and validation plan. A formally validated NGS-assay should be finalised before the implementation in routine practice. The laboratories should determine the optimal conditions for the test in order to meet the predefined minimal performance requirements (validation chapter). Iterative cycles should be performed until all assay conditions and analysis settings (test development chapter) meet the minimal predefined performance requirements. In case the latter cannot be reached, the lab should redetermine the minimal performance requirements and restart the procedure.

At each step of the test, critical parameters, quality metrics, their thresholds and their acceptable ranges should be defined. This development step will allow:

1) gaining the necessary experience with the test by identifying any critical step, parameter and quality metrics that may affect performance of the test,
2) interrupting the run prematurely before completion if significant deviations from the acceptance criteria are detected or if quality metric thresholds are not achieved, and
3) ensuring reliable NGS test results.[5,11] As quality metrics may vary between or even within laboratories, depending on the different platforms applied, each laboratory should establish its own quality metric thresholds.[2]

4.6.2 Wet bench part of the NGS process: DNA library preparation

There are different methods to prepare the DNA library for a targeted NGS analysis.[20] Each of them is a succession of a number of the following critical steps, depending on the assay used:

- DNA fragmentation

At first, DNA will be fragmented into DNA fragments of an optimal length determined by the downstream platform. Input mass of DNA and fragmentation conditions should be determined.

At the end of the fragmentation, two main quality metrics have to be measured and documented: (a) the size distribution of fragmented DNA samples and (b) the amount of fragmented DNA sample.[2,3] Both can be assessed by fragment analyser, spectrophotometric readings, gel image or real-time qPCR or similar instruments.

- cDNA synthesis

RNA first needs to be converted to first strand cDNA molecules, which serve as the proper template for library preparation. Additionally, cDNA fragmentation might also be required with subsequent quality analysis as described for DNA fragmentation.

- Target enrichment

a. Hybridization target capture allows the enrichment of the library with targeted regions. Biased capture can occur (e.g. in poor DNA quality sample) which is especially critical for equal representation of the different barcoded samples if pooled during DNA library preparation.[2,12]
b. Enrichment can also be achieved by amplification-based methods. Fragments are generated by PCR with primers targeting specific regions.

In general, hybridisation-based target capture is generally less sensitive but generates less false positives than PCR-based enrichments. It also generates a much more uniform horizontal coverage compared to PCR-based enrichment in which the coverage between amplicons can differ significantly.[21]

- Adapter and barcoding ligation

Platform-specific adapter sequences and sequencing primers will be ligated to both ends of the DNA.
If different DNA samples are pooled, barcodes are added to enable individual sample identification and to extract sequences obtained from a particular patient sample from the total data set. These barcodes consist of a unique DNA sequence having at least 1 bp difference between each other, typically three or more.[9] If every run contains the same targets, different barcode indexes should be used between consecutive runs in order to avoid sample leakage.[2] The number of samples that can be pooled should be determined during validation (validation chapter) and depends on the desired coverage read depth of the regions to be sequenced.[5,12]

- Tagmentation

The tagmentation method prepares genomic DNA libraries by using a transposase enzyme to simultaneously fragment and tag DNA by adding specific adapters to both ends of the fragments. These adapter sequences will amplify the insert DNA by PCR which adds index barcodes sequences.
Different parameters may be critical in the tagmentation method:

- The amount of DNA input: ratio of transposase complexes to sample DNA is critical in order to obtain transposition events separated by the appropriate distances.
- All reaction parameters, such as temperatures and reaction time, must be tightly controlled as the fragment size depends on the reaction efficiency.[20]

4.6.3 Normalisation

If DNA samples are pooled, normalisation should be performed in order to have equal representation of each sample. This can be achieved by diluting the DNA libraries to equal molarities based on fluorescence analysis, optical density measurement or qPCR. Alternatively, normalisation can be performed directly on beads.

4.6.4 Clonal amplification (if applicable)

Before the clonal amplification step, an optimal library quantity should be determined during the test development. An accurate estimation of the purified library quantity (e.g. DNA fragments with proper ligated adaptors and indexes) is crucial to obtain the optimal clonal amplification. Depending on the method used, optional quality and quantity controls can be performed at the end of the clonal amplification.

4.6.5 Sequencing

During this step, DNA library fragments and/or clonal amplicons thereof are sequenced on a flow cell by inferring eg. luminescence, fluorescence, pH, ionic current or impedance, which are then converted into sequences. Actual commercial platforms are based on different chemistries and each of them have specific parameters and test requirements.

4.6.6 Dry bench part of the NGS process or bioinformatics

The bioinformatics pipeline can be divided into three analytical steps: Primary analysis, secondary analysis and tertiary analysis. Tertiary analysis is discussed in chapter tertiary analysis.
Several bioinformatics pipelines may be evaluated during the development plan, separately and/or combined. Combination of two or more pipelines may result in a higher sensitivity and specificity than with the use of just one. This analysis should adequately be documented in the validation report.

4.6.7 Primary analysis

Primary analysis consists of different steps but not all of those are mandatory in this phase, since they can also be done later in the process; the selection of those should be defined during the validation process together with their corresponding quality metrics and thresholds:

- Base calling: the raw electronic information from the sequencer is converted into nucleotide positions, and quality scores are assigned to each base. This is performed by the instrument's algorithms. The laboratory has relatively limited control in this phase.
- Demultiplexing: when samples are pooled before the sequencing, the data must be assigned in silico to the sample of origin by comparing the index barcodes and the reference index set.
- Primer and adapter trimming: primers and adapters have to be trimmed from the obtained sequences in order to align them properly to the reference sequence and call variants.
- Low-quality base trimming: a base quality score (Q-score or Phred score) is assigned to each base that estimates the error probability for each base.[3,4,9] This is platform dependent and should be monitored during the run.[3]
- Read quality control: allows for checking whether the sequencing data is of sufficiently good quality to ensure variant calling analysis. Reads containing bases with many too low Q-scores should be removed by informatics filters before aligning to the reference sequence. If only the 3rd end of the read has low Q-scores, only this part of the read can be trimmed before alignment.[5] Too short reads after trimming should also be removed as it might cause problems during the mapping.

The outputs of the primary analysis phase are FASTQ files, which contain the succession of nucleotides with and their respective quality scores, for all the reads produced by the sequencer.[8,12]

4.6.8 Secondary analysis

This phase contains different steps. Again, not all of them are mandatory; the selection should be defined during the validation process together with their corresponding quality metrics and thresholds:

At DNA level:

- Reads contained in the FASTQ files (often 50–400 base pairs) are aligned to the reference sequence (read mapping), with software of choice which depends on local preferences and platforms. Mapping can be performed onto the target sequences or onto the full reference genome. Mapping to the whole reference sequence is preferred as it considerably reduces false-positive variant calls despite the fact that more computation time and space are required.[3]
- When a fragmentation or tagmentation step or amplicon-based technology is performed, duplicate reads resulting from clonal amplification should be removed by using informatics filters, as their inclusion generates a risk of skewing the allelic fractions. Keeping only the one with the highest quality score is recommended.[5]
- Indels should be evaluated on sufficient samples with insertions/deletions >15 bp and a local realignment should be evaluated to check if this additional step can improve the detection of indels.
- Base quality recalibration algorithms might be used to generate more accurate Q-scores.[5]

After these different steps, the output is the SAM (Sequence Alignment/Map) file, which is a tab-delimited text file that contains sequence alignment data, or the BAM file. It includes several types of information such as the mapped read sequences, base quality scores, mapping quality scores, and the position of insertions/

deletions/matches in the alignment.[8]

- Variant calling: once the reads are mapped, differences with the reference sequence are identified as SNVs or indels.

The output of this last part of the secondary analysis is the VCF file, which contains for each variant the chromosomal position, type of variant, coverage, allelic frequency, gene name and the quality scores.

These secondary analysis steps can be performed on or off the NGS instrument.[12]

During the test development, settings and quality metrics are determined and optimised in order to increase performance characteristics (validation chapter). Acceptable ranges and thresholds for each of these quality metrics should be defined and documented.[2,3,8,9] Settings are:

- Alignment settings (seed length, mismatch tolerance, mismatch penalties, gap penalties and gap extension penalties).
- Informatics filter settings which allow ignoring any read that map to non-targeted regions and analysing only reads mapping to the specific regions targeted.[5]

They are determined and optimised in order to increase the specificity (validation chapter) of the test. For example, by sequencing at the minimal coverage read depth (validation subchapter) a sufficient number of normal samples in which no variants are present, including low quality samples, and then adjusting the settings in order that no false-positives are detected.

Quality metrics are:

- Mapping quality scores which measure the uncertainty that a read is mapped properly to the reference sequence / genome.
- Proportion of duplicated reads (if appropriate).
- Coverage read depth of the region(s) of interest, which is the number of independent overlapping base calls. Coverage read depth threshold should be established during the validation to ensure adequate sensitivity (validation chapter) in the region(s) of interest.[2,3,5,9,12] Reference materials (general requirements for targeted NGS tests chapter) are preferably used to define the minimum coverage read depth for which additional coverage does not significantly improve the accuracy of the sequence (e.g. plotting the number of false positive and negative results as a function of coverage).[5] Variants not meeting the minimum coverage read depth should be tested by other methods or reported as not informative. Table or graph (e.g. histogram or box-and-whisker plot) of coverage read depths for each target area should be provided.[4]
- Average read coverage depth which is the average number of overlapping reads within the total sequenced area.[4]
- Allelic read percentage (also called variant allelic frequency (VAF)) which defines the percentage of variant reads in a background of normal reads. A minimum allelic read percentage should be equal to or higher than the limit of detection, which is determined during the validation process (validation chapter).[4,5]
- At RNA level:

RNA Fastq alignment to the human genome and mapping to genes can be performed by using different dedicated software programs.[22]

In order to assess that the sequencing run has performed correctly, some quality metrics can also be measured and their corresponding threshold should be determined during the validation plan. These metrics are platform specific and should be determined during the validation process.

- For example, for the Illumina platform, the optimal range of the cluster density (CD), which is the number of clones (or clusters) per mm^2 can be defined. Cluster density mostly depends on the concentration of the DNA library pool and should reach a minimal threshold in order to obtain a sufficient number of reads.
- If applicable, a threshold for the error rate, which is based on the sequence of a known spiked-in control

(e.g. PhiX), can be determined. The error rate is directly related to the Q-scores.

4.7. VALIDATION

4.7.1 General

Test validation is necessary to ensure that a new test is performing properly as intended for its clinical use. Desired performance characteristics should be defined in advance and integrated in the validation plan. The level of validation is function of the type of test.

Following the ISO 15189 norm, a validation is required for any new in-house (NGS) technology. The validation should apply to all intermediate steps of the entire (NGS) process and should include a deep investigation of the critical parameters defined in the test development, in order to detect any source of variation and interference and to verify that the desired performance criteria and requirements for process control are met. Before data analysis, the QC values of the NGS run need to meet the laboratory-defined thresholds. These parameters can include the cluster density (CD), pass filter (PF), %>Q30, and error rate (ER). At the sample level, QC values can include number of reads, % aligned, mean coverage for DNA, or mean expression of housekeeping genes for RNA analysis. Evaluation of laboratory-specific thresholds is required and if not met, consequences should be documented.

4.7.2 Performance characteristics

Performance characteristics include limit of detection, analytical sensitivity, specificity, precision and accuracy (see definitions). These characteristics should be empirically established and validated separately for each type of variant.[4,5]

These performance characteristics depend on several quality metrics described in the chapter on test development such as coverage read depth, allelic read percentage and base quality scores (Q-score) and on pipeline settings. The influence of the sample types on the performance characteristics should be considered.

4.7.3 Limit of detection

A crucial step in every validation plan is the establishment of the limit of detection (LOD). LOD can be assessed, for example, by dilution series of well-characterised samples with known mutations, or by using reference samples (for example HorizonDx samples in which different mutation types, at various VAF's ranging from 30% to less than 2%, in various genes are engineered).[12] This way of testing has the advantage that it may incorporate several confounding factors that may impede the LOD in daily practice. The dilution should be performed to the point that the variant of interest can no longer be detected. From these dilution series, the minimal required coverage read depth to detect a variant at desired VAF or supporting reads can be determined. For SNVs and indels, the limit of detection is usually around 5% of allelic frequency with a minimum of 15 (without UMI's) or 5 (with UMI's) reads with the alternative variant present. Deviations from these thresholds are allowed but need thorough validation. The minimal number of supporting fusion reads for gene fusions or exon skipping should be thoroughly validated. Note that this number can differ significantly between gene rearrangements. Low number of reads might indicate the presence of alternative rearrangements involving different exons of the same genes.

4.7.4 Analytical sensitivity and specificity

Analytical sensitivity and specificity are related to different quality metrics described in chapter 6. For example, the desired sensitivity and specificity may not be achieved when coverage read depth and base quality scores (Q-score) are below the threshold.[5]

Analytical sensitivity and specificity should be empirically established separately for each type of variant using

samples that are representative for the intended clinical sample type. Well-characterised reference materials (such as HorizonDx references) or clinical samples already analysed by another independent validated method such as Sanger sequencing, qPCR, FISH, or NGS by the same or another lab may be used.[4,5,8]
A sufficiently high number of variants and samples, adequately defined and representative for the clinical purpose, should be investigated in the validation process.[6] The numbers of tested variants will be smaller for smaller gene panels and higher for bigger ones.[23,24] Clinically important variants should be included as much as possible. Moreover, samples from different tumor types and specimens, and of varying quality and quantity should be included to mimic the sample input in the diagnostic NGS workup of the laboratory. A sensitivity of at least 95% and a specificity of at least 99% should be pursued.

4.7.5 Analytical precision

Repeatability can be established by sequencing the same sample (minimum three different samples) using different barcodes in triplicate at least under the same conditions in the same run.[4,5,7,8]
Reproducibility can be established by sequencing the same sample (minimum two different samples per variant type), in three different runs on the same instrument, or on different instruments if applicable (instrument variability), and by different technicians (inter operator variability).[3,4,7,8,12] The inter-operator reproducibility for the classification of variants should also be assessed. A repeatability and a reproducibility of at least 95% should be pursued.[12]

4.7.6 Analytical accuracy

Analytical accuracy should be established by sequencing well-characterised reference materials with multiple variants (that are representative for the intended clinical sample type) including those with allelic frequencies close to the established detection limits. In addition, the data obtained from the analytical sensitivity and specificity assays should be included. An analytical accuracy ≥99% should be pursued.

4.7.7 Validation of changes in the bioinformatics part only

Change in a part of the process, for example software updates or software changes, requires a validation of the particular bioinformatics part. In-house available data files or files from other NGS-accredited labs may be used.[2,4]
The validation can be achieved by using existing data, which are representative of the analysed tumour samples from at least 50 variants in 30 previously analysed samples (depending on the size of the panel, see above) with known variants of different types to verify that all the variants are still detected with the same analytical sensitivity, preferentially across a wide range of coverage levels. At the RNA level, at least 5 different gene fusions or exon skipping events should be tested. Preferably, reference samples or clinical samples with distinct known fusions should be included.
Assessment of the quality metrics should be done to ensure that no significant differences exist between the different software versions to enable the detection of all relevant variants.[2-4,9,12]
The software update release notes describing the modifications should be logged.

4.8. VERIFICATION

If performance specifications are available (for CE- marked IVD-compliant kits), the NGS test should be verified in their own laboratory in order to establish that specifications are met, in other words that the test is performing correctly as stated by the manufacturer. Moreover, critical quality metrics and parameters (test development chapter) should be measured.
The verification procedure is also applicable when minor modifications to the experimental protocol or to the

composition of the gene panel (e.g. when adding a new gene) of a validated workflow are performed.
For verification, at least 10 retrospective samples with known variants of different types should be tested and at least 10 variants detected in prospective samples should be confirmed by an independent reference method, which may be the original NGS method.[4]

4.9. QUALITY CONTROL

4.9.1 General

To ensure and maintain accurate test results, quality controls should be performed periodically at different levels:

- Internal Quality Control (IQC) should ensure that the process (instrument-reagents-operators) is working properly each time samples are processed. Procedures for IQC should cover checkpoints at different critical steps (by controlling quality metrics and quality parameters) and on the whole process (by determining performance characteristics).
- External Quality Assessment (EQA), with unknown material provided by a third party, should ensure that the performance of the laboratory itself and of the method used, complies with (inter)nationally accepted performance criteria.

4.9.2 Internal quality control

Procedures on internal quality control should be implemented by the laboratory to monitor the performance of the entire analytical process for each NGS test and its reproducibility over time. This should also allow for detecting errors or nonconformities during the process and eventually will indicate the need to interrupt the process if necessary.[5] The performance specifications and quality metric thresholds derived from the validation/verification process or from the manufacturer will be used to assess the validity of each test run.

4.9.3 Quality control materials

- Positive controls

A positive control, such as an engineered DNA/RNA reference material, should be included to assess the NGS test on a regular basis and at critical steps (for example when starting a new lot of critical reagents) and should contain multiple known somatic variants of different types, preferably near the limit of detection of the assay in order to assess that low percentage variants can reproducibly be identified.[2,4,5]
The frequency of analysing positive controls should be based on the stability of the procedure and the risk of harm to the patient from an erroneous result.[1] Particularly for sequencing, evaluating predefined run quality metrics may be adequate to assure the validity of each single run, making the analysis of a positive control in each run superfluous.
Laboratories should document the use of positive controls and monitor the results over time.

- Negative controls

It is advised to include a no-template control during the PCR steps within the template preparation to check for sample contamination.[4,9]
Moreover, data analysis can be performed to check if reads are generated from a barcode used in the previous run (leakage) and not in the current run and if reads are generated for targets not included in the current run. Different mutational profile for each sample is a strong indication that there is no sample contamination, making the use of negative control superfluous.

- Performance monitoring

The performance measures determined in the validation process (validation chapter) should be recorded in the validation/verification report (validation/verification report subchapter) and in subsequent routine

diagnostic runs. Comparison to those of an optimal validated run can be used to monitor the reproducibility and the overall quality.[2]

- Quality metrics monitoring

Quality metrics should be monitored at each run and routinely collected and compared to those of an optimal validated run.[2]

Any significant deviations should be investigated and may require repeating the test.[2,5] It can also help in defining the source of the problem in an underperforming test.[2,4]

- External quality control

Proficiency testing (PT) and EQA should be performed periodically at least once a year to monitor the test performance, by analysing well-defined materials provided by an independent third party but unknown to the laboratory.[2] Laboratories should share with each other well-characterised samples and data files to collaboratively improve and standardise NGS testing.[8]

4.10. TERTIARY ANALYSIS

For chapters 4.10 and 4.11 more details can be found in the publication in Cancers 2019.[25]

Yes

Based upon secondary analysis data, tertiary analysis is mainly composed of two different steps: (1) the annotation and the biologic classification of the identified sequence variants and (2) their clinical classification and their clinical utilities annotations. This part is performed off-instrument.

1) Each variant should be annotated with dedicated software that annotates each variant in relation to its position in the gene (exonic, coding, amino acid change, etc.), classified into 5 biologic classes (cfr 4.11.2), following a systematic and documented procedure which should be described in the traceability documents and be part of the quality system.
2) Secondly, each variant should be classified into 4 clinical classes (cfr 4.11.3) and annotated with their clinical utilities (diagnostic, prognostic or therapeutic). Clinical classification and clinical utilities annotations are based on literature search and screening into different database (such as Cosmic, dbSNP, My Cancer Genome, ClinVar, Civic, MD Anderson) and both should be discussed within a post-analytical discussion forum, also called Molecular Advisory Board (MAB) (national or local) (composed of clinicians, pathologists, molecular geneticists, etc.). The functionality of the MAB should be adequately documented.

Figure 2a + addendum describes the workflow for the biological classification of somatic variants identified at DNA level (v1). Table 1 gives an overview of the variant classification scoring table with exceptions.

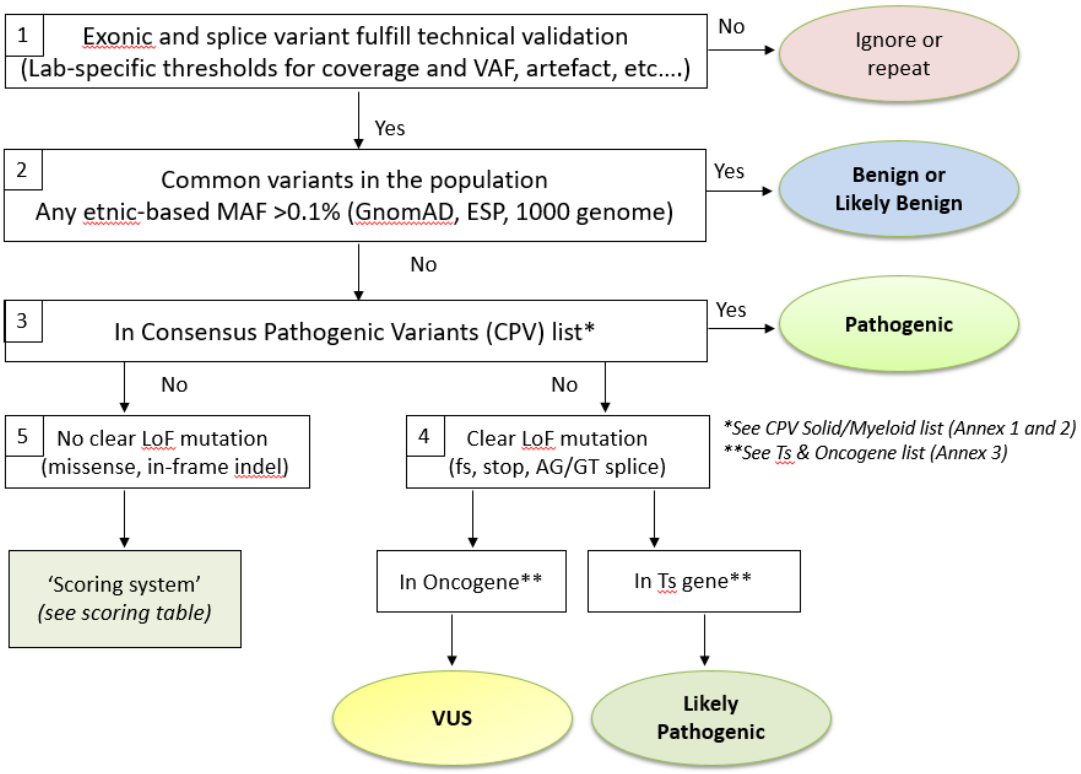


Figure 2a: Workflow for the biological classification of somatic variants (v1). Note that for calling a variant as being (Likely) Benign based on the minor allele frequency (MAF) in an etnic population (e.g. GnomAD), a minimum of 2000 alleles must have been analysed. [24]

Table 1: Variant classification Scoring Table

Parameter	Score +2	Score +1	Score +0.5	Score 0	Score -1
Total # of entries of that particular AA change at that position in COSMIC	Solid: ≥50	50 > x > 10	/	≤10	/
	Hemato: ≥10	*10 > x > 5*	/	*≤5*	/
In silico prediction tools SIFT and MutationTaster	/	/	Both damaging and deleterious	Other	/
Harmful in functional studies (PubMed, JAX-CKB, MDA, MCG)	/	/	Yes	Not reported	No
Described in at least one genomic db (CIVIC, ClinVar, OncoKb, VarSome)	/	/	As (Likely) Pathogenic	Not described /unknown	As (Likely) Benign

Variants with a **score ≥2** will be classified as '**Likely Pathogenic**'

Variants with a **score < 2** are classified as '**VUS**'

Remarks:

- All variants that are eligible for the Scoring Table should be analyzed for all four parameters of this system, irrespective of the number of COSMIC entries. This way, specific (novel) findings on that variant might alter the class that is obtained via the Scoring Table. Expert knowledge therefore can 'overrule' the scoring-based classification.
- Special attention should be given to combination of variants (eg. resistance variant in combination with an activating variant).

Exceptions to the workflow v2

1. Somatic missense or in-frame indel variants in **TP53** are not scored via the standard ComPerMed workflow but their functional effect have to be checked in IARC (http://p53.iarc.fr/) and Seshat (http://vps338341.ovh.net/).
2. "Clear **LoF** (fs, stop, splice site) variants in the tumor suppressor genes **BRCA1** and **BRCA2** are classified as Pathogenic instead of Likely Pathogenic. Notably, LoF variants in the last exon as well as all other somatic variants need to be checked for their pathogenicity in different online databases including ARUP (http://www.arup.utah.edu/database/BRCA/), InterVar (http://wintervar.wglab.org/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Enigma (https://brcaexchange.org/) and LOVD (https://databases.lovd.nl/shared/genes)."
3. The c.1934dup in the **polyG** stretch of **ASXL1** is 'Likely Pathogenic' only if the variant allele frequency (VAF) is significantly higher than that obtained for the polyG stutter error, which is method specific.
4. **Splice site** variants should at least be checked at the -2, -1 and +1, +2 exon flanking positions, which harbor the AG/GT consensus splice motif. Flanking intronic positions that could affect splicing need to be investigated at least for:

- **MET** intron 13 and intron 14 deletions, which affect **exon 14** skipping
- **KIT** intron 10 deletions, which result in partial **exon 11** skipping
- splice regions in **BRCA1** and **BRCA2** that have been shown to affect splicing

All splice site variants in tumor suppressor genes are considered as **LoF** variants obtaining the class Likely Pathogenic, except those in BRCA1, BRCA2, MET exon 14 skipping and KIT partial exon 11 skipping, which are all regarded as Pathogenic.

5. **CALR** exon 9 type I and type II out-of-frame indels have to be classified as Pathogenic.
6. **FLT3** exon 14 in-frame internal tandem duplications (ITD) and **NPM1** exon 11 out-of-frame ITD's or insertions have to be classified as Pathogenic.
7. Somatic in-frame indels in the bZIP domain of **CEBPA** should be regarded as Likely Pathogenic. Moreover, the combination of a clear LoF (fs, stop, splice site) variant in the N-terminal part of CEBPA with an in-frame change in the bZIP domain (C-terminal part) should be classified as Pathogenic.
8. A variant of unknown significance (VUS) that occurs at least twice in different patients in the internal database at germline VAF should be evaluated for being a **rare SNP** (single nucleotide polymorphism).

In-depth knowledge on the specifics of each database is crucial for correct analysis of variants.

The classification of gene fusions and exon skipping events at the RNA level has to be performed according to the gene fusion classification workflow (Figure 2b). Independent of the RNA analysis software the genomic positions of the breakpoints of gene rearrangements are always provided together with the number of supporting reads for that fusion. Often, additional information such as the gene(s) in which they reside including the transcript ID, the orientation, exon number etc. are provided as well. As a first quality check each rearrangement needs to be assessed for the number of supporting fusion reads, which should exceed the validated threshold. For fusions with supporting reads that exceed the threshold, their presence in the Common fusion gene list, which only includes the most common ones in solid and hematological tumors (see Annex 4), is checked. Moreover, special attention has to be given to the breakpoint positions. The rearrangements present in the Common gene fusion list with recurrent breakpoints are classified as Pathogenic. For all detected gene fusion events the genomic positions of both breakpoints have to be visualized in a genome browser, e.g. IGV. These breakpoints should preferentially map to an exon boundary, or in a few cases within an intron close to an exon, within an exon or in a 5'UTR (gene promoter) and should be able to deliver a potential functional fusion gene with an in-frame fusion in the correct orientation, often with retention of relevant domains (dimerization, kinase, …). If one of these criteria is not fulfilled (e.g. breakpoint located deeply within an intron or an intragenic region or definitely yielding no functional fusion protein) these fusions should not be retained. Potentially correct fusions should be further analyzed in cancer-specific gene fusion databases such as the Fusion Gene Annotation Database (FusionGDB; https://ccsm.uth.edu/FusionGDB/index.html), the Atlas of Genetics and Cytogenetics in Oncology and Haematology (http://atlasgeneticsoncology.org/Tumors/softissuTumID5042.html) or the Mitelman Database (https://mitelmandatabase.isb-cgc.org/) providing information on functional domain retention. Moreover, the literature should be checked as well for the (potential) relation or involvement of the fusion in tumorigenesis. If sufficient tumor-related evidence is available these fusions can be classified as Pathogenic or Likely Pathogenic, depending on the strength of the supporting information.

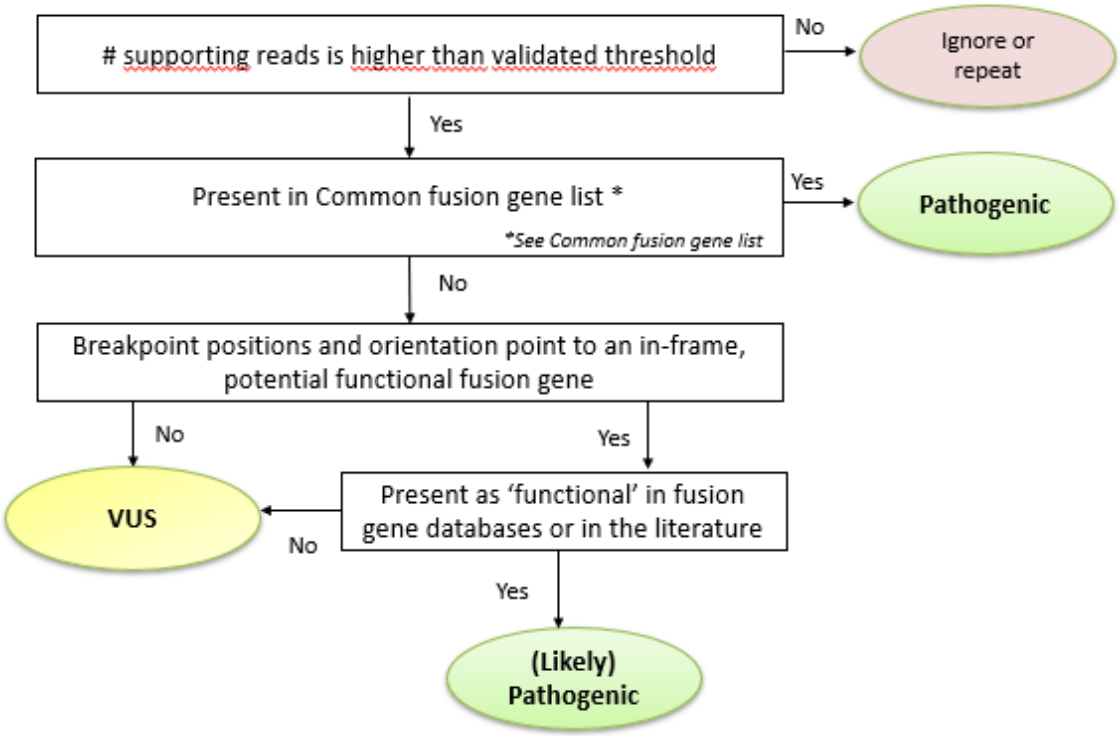


Figure 2b. Workflow for the biological classification of fusion genes (v1).

4.11. REPORTING

4.11.1 Variant annotation

It was decided to use the HGVS annotation (http://www.hgvs.org/) published by 'den Dunnen et al. Hum Mutat 2016'.

Special attention: the protein annotation has to be between brackets e.g. p.(Val600Glu) to indicate that the variant was found at DNA level only.

The 3-letter code for the amino acid has to be used in the results section (recommendation of HGVS) but the one letter code can also be added between brackets e.g. p.(Val600Glu) (V600E).

Use '*' instead of 'Ter'. HGVS allows both but we reached a consensus terminology. E.g. p.(Cys102*) to describe a stop codon, or p.(Cys102Tyrfs*13) to describe a frameshift.

Positions are based on the NM_ number of the main transcript.

4.11.2 Biological classes

There is a general consensus to use these 5 biological classes:

Biological class	Reporting
Pathogenic	must be reported
Likely pathogenic	must be reported
VUS	must be reported clearly separated from pathogenic and likely pathogenic variants, but should not be clinically discussed
Likely benign	should not be reported
Benign	should not be reported

This classification is based on the ACMG and AMP Standards and Guidelines publication of Richards et al. Genet Med 2015, even though these guidelines are meant for germline variants.

Remarks:

Pathogenic and likely pathogenic biological classes are present in the clinical report in the section 'Test results'. VUS variants can be in the 'Test results' section, clearly separated from the other variants or at the end of the report.

As the clinical report is written in the hospital's language, it was decided to translate 'likely pathogenic' in:

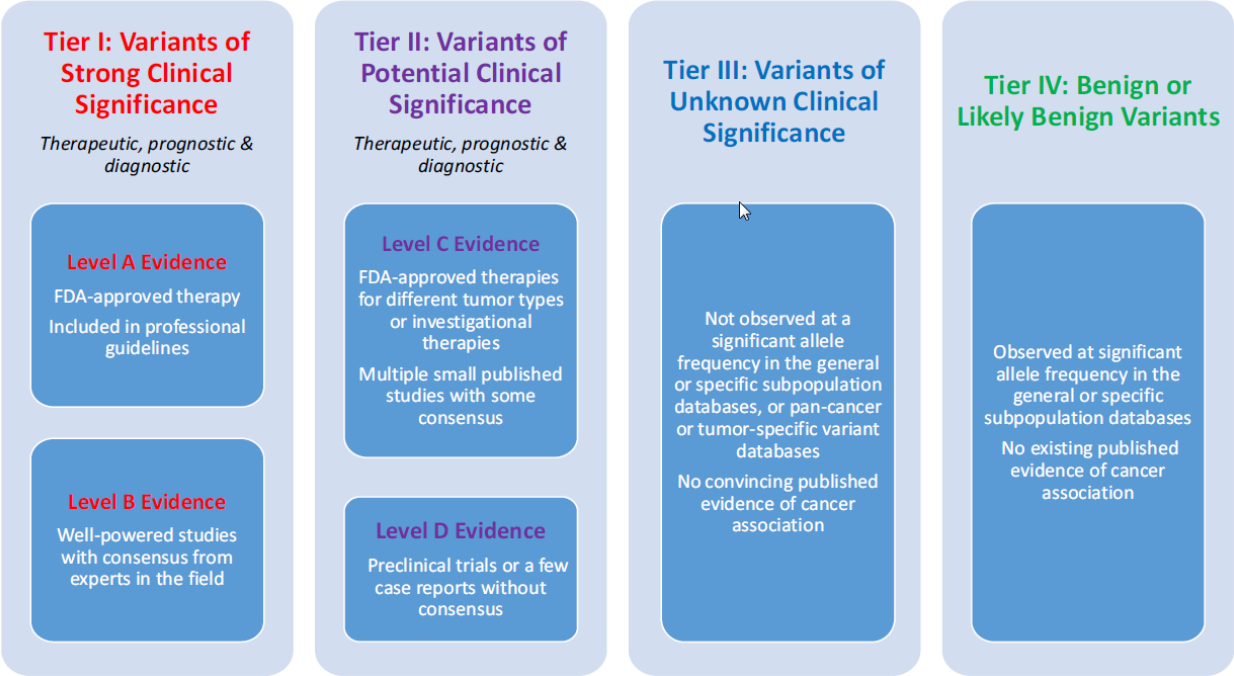
French → Probablement pathogénique
Dutch → Vermoedelijk pathogeen
German → Wahrscheinlich pathogen

4.11.3 Clinical classes

There is a general consensus to use 4 clinical classes:

Clinical class	Reporting
Tier I: Strong clinical significance	Tier I must be discussed in the conclusion of the clinical report.
Tier II: Potential clinical significance	Tier II must be discussed in the conclusion of the clinical report.
Tier III: Unknown clinical significance	Tier III must be discussed in the conclusion of the clinical report (except for a VUS).
Tier IV: variants deemed benign or likely benign	should not be reported

This classification is based on the ACMG and AMP Standards and Guidelines publication of Li et al. J Mol Diagn 2017.



Categories of Clinical and/or Experimental Evidence

Category	Therapeutic	Diagnosis	Prognosis
Level A	1. Biomarkers that predict response or resistance to FDA-approved therapies for a specific type of tumor 2. Biomarkers included in professional guidelines that predict response or resistance to therapies for a specific type of tumor	Biomarkers included in professional guidelines as diagnostic for a specific type of tumor	Biomarkers included in professional guidelines as prognostic for a specific type of tumor
Level B	Biomarkers that predict response or resistance to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field	Biomarkers of diagnostic significance for a specific type of tumor based on well-powered studies with consensus from experts in the field	Biomarkers of prognostic significance for a specific type of tumor based on well-powered studies with consensus from experts in the field
Level C	1. Biomarkers that predict response or resistance to therapies approved by the FDA or professional societies for a different type of tumor 2. Biomarkers that serve as inclusion criteria for clinical trials	Biomarkers of diagnostic significance based on the results of multiple small studies	Biomarkers of prognostic significance based on the results of multiple small studies
Level D	Biomarkers that show plausible therapeutic significance based on preclinical studies	Biomarkers that may assist disease diagnosis themselves or along with other biomarkers based on small studies or a few case reports	Biomarkers that may assist disease prognosis themselves or along with other biomarkers based on small studies or a few case reports

FDA, Food and Drug Administration.

Clinical classes (Strong clinical significance (Tier I), Potential clinical significance (Tier II) and Unknown clinical significance (Tier III)) are present in the clinical report in the section 'Conclusions and interpretation of the report' (see below).

Remark: VUS variants are always considered as a Tier III class.

French translation:

Clinical class	Reporting in French
Tier I: Strong clinical significance	Impact clinique avéré
Tier II: Potential clinical significance	Impact clinique potentiel
Tier III: Unknown clinical significance	Impact clinique indeterminé

Dutch translation:

Clinical class	Reporting in Dutch
Tier I: Strong clinical significance	Significant klinisch belang
Tier II: Potential clinical significance	Mogelijk klinisch belang
Tier III: Unknown clinical significance	Ongekende klinische betekenis

German translation :

Clinical class	Reporting in German
Tier I: Strong clinical significance	Relevante klinische Bedeutung
Tier II: Potential clinical significance	Mögliche klinische Bedeutung
Tier III: Unknown clinical significance	Unbekannte klinische Bedeutung

Since most labs in Belgium are not using the Tier level system for clinical variant reporting, their inclusion in reports is still under discussion.

4.11.4 Clinical report

The clinical report should contain the following information, in the hospital's language:

4.11.4.1 Laboratory, patient and physician identification

As required by the ISO15189 norm, laboratory, patient and physician identification should be reported.

4.11.4.2 Medical information

The following information is required, if applicable for the tumor type, but can be presented in a different format.

Primary tumor type and histology	e.g. NSCLC, adenocarcinoma e.g. Acute myeloid leukemia
Clinical Information and Request	e. g. stage of tumor, treatment phase, therapy considered, …

4.11.4.3 Sample information

The following information is required, if applicable for the tumor type, but can be presented in a different format.

Sample ID (primary lab)	XXXX
Sampling date	e.g. 24-09-2018

Date of sample received	e.g. 01-10-2018
Sample tumoral stage	Primary/metastasis
Sample anatomic site	e.g. colon, lung, liver, blood, pleural cavity, bone marrow, axillary lymph node …
Sample type	eg. Resection, (endoscopic) biopsy, fluid, aspirate, trephine biopsy …
Sample procedure	e.g. FFPE, frozen tissue, fresh tissue;…
Neoplastic cells (%)	e.g. 10
Sample quality	Disclaimer if sample does not fulfill pre-analytical requirements

4.11.4.4 Test results

A table format is preferred but is not mandatory.

For somatic variants identified at DNA or RNA level

Gene name	HGVSc annotation*	HGVSp annotation**	Biological class	Allelic freq (%)
EGFR	c.2573T>G	p.(Leu858Arg) (L858R)	Pathogenic	5

Non interpretable results:
List them (only the hotspot, or specify that gene xxx was not totally covered) and explain the reason (due to insufficient coverage, below the validated threshold/….)
Analysis not possible:
explain the reason (no or insufficient material / necrosis / DNA quality too low/ failed library prep / …)

Remarks:

- NM_refs (versioned) have to be specified either in the Method (see part 8) or here in this table.
- Genomic position should not be included.
- *For SNV/indel variants detected at the RNA level the annotation should be c.(2573T>G) in which the brackets indicate that the variant was not detected directly on DNA.
- **The use of the three-letter AA code is obligatory. The one-letter AA code may also be included. Therefore, in the Table above, (L858R) may be included in the 'HGVSp annotation' cell.

For gene rearrangements identified at the RNA level, only the (Likely) Pathogenic fusions or exon skipping events should be included. A table format is preferred but is not mandatory.

Fusion gene/Exon skip	Chr aberr	Transcript A	Exon A	Transcript B	Exon B
EML4-ALK	t(2;2)	NM_019063.5	Exon 6	NM_004304.5	Exon 20
METex14 skipping	Chr7	NM_001127500.3	Exon 13	NM_001127500.3	Exon 15
BCR-ABL1	t(9;22)	NM_004327.4	Exon 14	NM_005157.6	Exon 2

Analysis not possible:
explain the reason (no or insufficient material / necrosis / RNA quality too low / failed library prep / …)

Remarks:
- A hyphen (-) is used to separate the gene partners (cfr. HGVS nomenclature)
- Genomic positions or useful additional information might be added e.g. var3a, minor e1-a2
- Additional information that describes the breakpoint position is indicated by '::'.
  E.g. exon 6::exon20, chr22:23524426::chr9:133729451 (cfr. HGVS nomenclature)

4.11.4.5 Standardization of conclusions of the clinical report

The clinical report should contain the conclusion and clinical interpretation of each pathogenic and likely pathogenic variant.

It is recommended to be as concise and specific as possible in the conclusions' description and to use systematically the same order of appearance of information (see order's description below). We also recommend using the same keywords for each report.

Each variant has to be accompanied with their clinical significance (strong clinical significance, potential clinical significance or unknown clinical significance) and with their clinical impact (involved in diagnosis, involved in prognosis, involved in therapy). We also recommend to indicate in which pathology this clinical significance is described.

For variants involved in therapy, we strongly recommend to specify whether it is the standard treatment or a relevant clinical study, and to specify if the clinical study is well-powered or in progress. In case of the absence of variants which confer resistance to a standard treatment (e.g. CRC without KRAS mutation), the indication for this standard treatment, linked to the absence of this mutation, has to be indicated.

The combined effect of multiple variants should also be discussed in the conclusions.

References should be added and provided in an unequivocal manner (e.g. Li et al 2016 J Mol Diagn; or, PMID 27993330).

Order of appearance of information in the report's conclusions, if applicable:

1. Diagnostic conclusion
2. Prognostic information for this pathology
3. Indication or absence of indication for standard treatment for this pathology
4. Relevant clinical studies well-powered or in progress for this pathology
5. Information on identified genes/variants with clinical interest. E.g. constitutive activation of the RAS cascade, mutated exon only in case of clinical utility (e.g. KIT exon 11)
6. Combined effect of variants or biomarkers

4.11.4.6 Identification of the person(s) who interpret and/or validate the results of the analysis

As required by the ISO 15189 norm.

4.11.4.7 Date of the report

As required by the ISO 15189 norm.

4.11.4.8 Methods

The following information is required either in this part of the clinical report or on the laboratories web site with a referral in the report to the website. The referral should mention a version number of the information (e.g. 'Information for patients and users- version XX').

- Brief method for the wet and dry lab analyses (kit and software names and versions)
- Sequencer reference (e.g. MiSeq, Ion GeneStudio S5, ...)
- Limit of detection (VAF threshold, ...)
- List of genes and exons analyzed (e.g. BRAF exons 11 and 15; DNMT3A all coding exons; …) with NM_ accession numbers with version (e.g. NM_00522.3)
- List of all exons or regions having insufficient coverage in most samples (e.g. DNMT3A exon 6 AA165-184; TET2 exon 4; …) .
- Reference genome used (e.g. Hg19).
- A disclaimer that states that this NGS test cannot differentiate between somatic and germline variants.

4.12. TURNAROUND TIME

The turnaround time for the entire NGS analysis from biopsy to reporting should be appropriate for the intended clinical purpose and in agreement with the tumour specific guidelines, if available, though in general a turnaround time of ≤15 working days is highly recommended.

4.14. REFERENCES

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Annex 1: Consensus Pathogenic Variants (CPV) in the Convention genes of solid and hematological tumors v2

Annex 2: Consensus pathogenic variants (CPV) of TSO500 panel (v4)

Annex 3: Tumor suppressor (TsG) & Oncogene list of TSO500 panel (v1)

Annex 4: Common fusion gene list (v1) ***(not yet complete)***

Annex 1: Consensus Pathogenic Variants (CPV) in the Convention genes of solid and hematological tumors v2

Changes made to v1 are indicated in red

Gene	Transcript ID	Hs1	Hs2	Hs3	Hs4	Hs5	Hs6	Hs7	Hs8	Hs9	Hs10	Hs11	Hs12	Hs13	Hs12	Hs13
ASXL1	NM_015338.5	*none*														
BRAF	NM_004333.5	G469A/E/R/V	D594G/N	T599-K601if-del/ins	V600E/K/M/R	K601E										
BRCA1	NM_007294.3	all clear LoF variants (nonsense, frameshift, splice site)														
BRCA2	NM_000059.3	all clear LoF variants (nonsense, frameshift, splice site)														
BTK	NM_000061.2	C481S														
CALR	NM_004343.3	ex9of-del	ex9of-ins													
CBL	NM_005188.3	*none*														
CEBPA	NM_004364.3	*none*														
CSF3R	NM_156039.3	T618I														
DNMT3A	NM_ 175629.2	R882C/H														
EGFR	NM_005228.4	G719A/C/S	ex19if-del/ins	ex20if-ins	T790M	C797S	L858R	L861Q								
ERBB2	NM_004448.3	S310F/Y	R678Q	L755S	Y772_A775 if-dup	V777L	V842I	P1170A								
ESR1	NM_000125.3	K303R	E380Q	~~V392I~~	S463P	V533M	V534E	P535H	L536H/P/Q/R	Y537C/N/S	D538G					
EZH2	NM_004456.4	Y646F/H/N/S														
FLT3	NM_004119.2	ex14if-dup	D835A/E/H/V/Y	Y842C												
GNAS	NM_080425.4	R844C/H (R201C/H in NM_000516)														
H3F3A	NM_002107.4	K28M	G35R/W													
HRAS	NM_005343.3	G12C/D/S/V	G13C/D/R/S/V	Q61H/K/L/R												
IDH1	NM_005896.3	R132C/G/L/H/S														
IDH2	NM_002168.3	R140L/Q/W	R172K/M/S													
JAK2	NM_004972.3	ex12 if-del/if-dup	V617F													
KIT	NM_000222.2	ex8 D419if-del	ex9 S501-F504if-ins	ex11 K550-E561if-indel	ex11 W557G/R	ex11 V559A/D	ex11 V560D/del	ex11 L576P	ex13 K642E	ex13 V654A	ex14 T670I	ex17 D816H/V/Y	ex17 N822K	ex17 Y823D		
KRAS	NM_004985.4	G12A/C/D/F/R/S/V	G13C/D/R/S/V	A59T	Q61H/K/L/R	K117N	A146T									
MET	NM_001127500.2	ex14 skipping														
MPL	NM_005373.2	S505N	W515A/K/L/R/S													
NPM1	NM_002520.6	ex11of-ins														
NRAS	NM_002524.4	G12A/C/D/R/S/V	G13C/D/R/S/V	~~A59T~~	Q61H/K/L/R	~~K117N~~	A146T									
PCLG2	NM_002661.3	*none*														
PDGFRA	NM_006206.5	V561D	S566_E571if-del	D842V	D842_I843if-del											
PIK3CA	NM_006218.3	E81K	R88Q	R108H	G118D	N345K	I391M	C420R	E453K	E542K	E545A/D/G/K/R/Q/V	Q546K/P/R	E726K	M1043I	H1047L/R	G1049R
RUNX1	NM_001754.4	*none*														
SETBP1	NM_015559.3	D868N	G870S													
SF3B1	NM_012433.3	E622D	R625C/H/L	H662Q	K666N/R/T	K700E	G742D									
SRSF2	NM_003016.4	P95H/L/R	P95_R102del													
TET2	NM_001127208.2	*none*														
TP53	NM_000546.5	R175H	Y220C	G245S	R248Q/W	R273C/H	R282W									
U2AF1	NM_006758.2	S34F/Y	Q157P/R													
WT1	NM_024426.5	*none*														

if-del: inframe deletion; if-ins: inframe insertion; if-dup: inframe duplication; of-del: out of frame deletion; of-ins: out of frame insertion; _ : denotes the exact positions of that change; - : denotes a region in which the change has to be located; none: no consensus pathogenic variants present

Annex 2: Consensus pathogenic variants (CPV) of TSO500 panel (v4)

Consensus pathogenic variants (CPV) in the 523 genes of the TSO500 panel (v4)

Changes compared to v2 Changes compared to v3

Gene	Transcript ID	Hs1	Hs2	Hs3	Hs4	Hs5	Hs6	Hs7	Hs8	Hs9	Hs10	Hs11	Hs12	Hs13	Hs14
ABL1	NM_007313.2	T334I													
AKT1	NM_005163.2	E17K													
ALK	NM_004304.4	F1174L	R1275Q												
AR	NM_000044.6	Q58L	L702H	H875Y	T878A										
ATM	NM_000051.3	N1983S													
ATRX	NM_000489.5	Q929E													
AXL	NM_021913.5	N266D													
BCOR	NM_001123385.1	N1425S													
BRAF	NM_004333.5	G469A/E/R/V	D594G/N	T599-K601if-del/ins	V600E/K/M/R	K601E									
BRCA1	NM_007294.3	all clear LoF variants (nonsense, frameshift, splice site)													
BRCA2	NM_000059.3	all clear LoF variants (nonsense, frameshift, splice site)													
BTK	NM_000061.2	C481S													
CALR	NM_004343.3	ex9 of-del	ex9 of-ins												
CDKN2A	NM_000077.4	H83Y	P114L												
CEBPA	NM_004364.3	K313dup													
CHEK2	NM_007194.3	K373E													
CSF3R	NM_156039.3	T618I													
CTNNB1	NM_001904.4	A5_A80 if-del	D32A/G/H/N/V/Y	S33A/C/F/P/Y	G34E/R/V	I35S	H36P	S37A/C/F/P/Y	T41A/I	S45 if-del /A/C/F/P/Y					
DICER1	NM_177438.3	E1705K	D1709N												
DNMT3A	NM_175629.2	R882C/H													
EGFR	NM_005228.4	A289V	G719A/C/S	ex19if-del/ins	ex20if-ins	T790M	C797S	L858R	L861Q						
ERBB2	NM_004448.3	S310F/Y	R678Q	L755S	Y772_A775 if-dup	V777L	V842I								
ERBB3	NM_001982.4	V104L/M													
ERCC2	NM_000400.3	D312N													
ESR1	NM_000125.3	K303R	E380Q	S463P	V533M	V534E	P535H	L536H/P/Q/R	Y537C/N/S	D538G					
EZH2	NM_004456.4	Y646F/H/N/S													
FBXW7	NM_001349798.2	R465C/H	R479Q	R505C/G											
FGFR2	NM_022970.3	S252W													
FGFR3	NM_001163213.1	R248C	S249C	G372C	S373C	Y375C	K652E/M								
FLT3	NM_004119.2	ex14 if-dup	D835A/E/H/V/Y	Y842C											
FOXL2	NM_023067.4	C134W													
GNA11	NM_002067.5	Q209L													
GNAQ	NM_002072.5	Q209L/P													
GNAS	NM_080425.4	R844C/H (R201C/H in NM_000516)													
H3F3A	NM_002107.4	K28M	G35R/W												
HIST1H3B	NM_003537.4	K28M													
HRAS	NM_005343.3	G12any-ms	G13any-ms	Q61H/K/L/R											
IDH1	NM_005896.3	R132C/G/L/H/S													
IDH2	NM_002168.3	R140L/Q/W	R172K/M/S												
JAK2	NM_004972.3	ex12 if-del/if-dup	V617F												
JAK3	NM_000215.4	M511I													
KIT	NM_000222.2	ex8	ex9	ex11	ex11	ex11	ex11	ex11	ex13	ex13	ex14	ex17	ex17	ex17	
		D419if-del	S501-F504if-ins	K550-E561if-indel	W557G/R	V559A/D	V560D/del	L576P	K642E	V654A	T670I	D816H/V/Y	N822K	Y823D	
KLF4	NM_004235.6	K409Q													
KMT2C	NM_170606.3	D348N													
KRAS	NM_004985.4	G12any-ms	G13any-ms	A59T	Q61H/K/L/R	K117N	A146T								
MED12	NM_005120.3	L36R	Q43P	G44A/C/D/R/S/V											
MET	NM_001127500.2	ex14 skipping													
MPL	NM_005373.2	S505N	W515any-ms												
MST1R	NM_002447.4	S1195G													
MYCN	NM_005378.6	P44L													
MYD88	NM_001172567.1	L273P (L265P in NM_002468)													
NOTCH1	NM_017617.5	R1598P	L1600P	L1678P											
NPM1	NM_002520.6	ex11 of-ins													
NRAS	NM_002524.4	G12any-ms	G13any-ms	A59T	Q61H/K/L/R	A146T									
PDGFRA	NM_006206.5	V561D	S566_E571if-del	D842V	D842_I843if-del										
PIK3CA	NM_006218.3	E81K	R88Q	R108H	G118D	N345K	C420R	E453K	E542K	E545any-ms	Q546K/P/R	E726K	M1043I	H1047L/R/	G1049R
PIK3R2	NM_005027.4	S313P													
PIK3R3	NM_003629.4	N329K													
POLE	NM_006231.4	P286R	V411L												
PPP2R1A	NM_014225.6	P179R	R183W												
PTEN	NM_000314.8	R130G/L/Q	R173C/H												
PTPN11	NM_002834.5	D61V/Y	A72T/V	E76G/K											
RAC1	NM_018890.4	P29S													
RET	NM_020975.6	M918T													
RHOA	NM_001664.4	G17V													
SETBP1	NM_015559.3	D868N	G870S												
SF3B1	NM_012433.3	E622D	R625C/H/L	H662Q	K666N/R/T	K700E	G742D								
SMAD4	NM_005359.6	R361C/H													
SMO	NM_005631.5	L412F													
SRSF2	NM_003016.4	P95H/L/R	P95_R102del												
STAT3	NM_139276.3	Y640F	D661Y												
TGFBR2	NM_001024847.2	R553H													
TP53	NM_000546.5	R175H	Y220C	G245S	R248Q/W	R273C/H	R282W								
U2AF1	NM_006758.2	S34F/Y	Q157P/R												
XPO1	NM_003400.4	E571K													

if-del: inframe deletion
if-ins: inframe insertion
if-dup: inframe duplication
of-del: out of frame deletion
of-ins: out of frame insertion
_ : denotes the exact positions of that change
- : denotes a region in which the change has to be located

Annex 3: Tumor suppressor (TsG) & Oncogene list of TSO500 panel (v1)

Gene	Onco/TsG	Merge		Vogelstein	Jax CKB	cell signal	MSK paper	Census Sanger	ONGene	TsG Db	OncoKb	Vanderbilt	Intogen	Cancermine
ABL1	Oncogene	Oncogene (9)		Oncogene	Oncogene		Oncogene	Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	Oncogene
ABL2	Oncogene	Oncogene (7)			Oncogene		Oncogene	Oncogene	Oncogene		Oncogene		Oncogene	Oncogene
ACVR1	Oncogene	Oncogene (2)			unknown			Oncogene			Oncogene		unknown	
ACVR1B	TsG	TsG (1)		TsG	unknown									
AKT1	Oncogene	Oncogene (8)		Oncogene	Oncogene		Oncogene	Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	unknown
AKT2	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene	Oncogene		Oncogene	Oncogene		unknown
AKT3	Oncogene	Oncogene (3)			Oncogene			Oncogene			Oncogene		unknown	unknown
ALK	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	unknown
ALOX12B	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						Oncogene, TsG			
ANKRD11	TsG	TsG (2)			unknown						TsG			TsG
ANKRD26					unknown									
APC	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
AR	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	unknown
ARAF	Oncogene	Oncogene (7)			Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	Oncogene
ARFRP1					unknown									
ARID1A	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
ARID1B	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
ARID2	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
ARID5B	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG			Oncogene
ASXL1	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
ASXL2	TsG	TsG (5)			TsG			TsG			TsG		TsG	TsG
ATM	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
ATR	TsG	TsG (6)			TsG	TsG		TsG		TsG	TsG	TsG		
ATRX	TsG	TsG (6)		TsG	TsG			TsG			TsG		TsG	TsG
AURKA	Oncogene	Oncogene (3)			unknown				Oncogene		Oncogene	Oncogene		unknown
AURKB	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
AXIN1	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
AXIN2	TsG	TsG (6)			TsG			TsG		TsG	TsG	TsG	TsG	
AXL	Oncogene	Oncogene (3)			unknown				Oncogene		Oncogene	Oncogene		unknown
B2M	TsG	Oncogene (1) / TsG (5)		TsG	TsG			TsG			TsG		TsG	Oncogene
BAP1	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
BARD1	TsG	Oncogene (1) / TsG (6)			TsG			TsG	Oncogene	TsG	TsG	TsG		TsG
BBC3	TsG	TsG (2)			unknown					TsG	TsG			unknown
BCL10	TsG	TsG (4)			unknown			TsG		TsG	TsG	TsG	unknown	
BCL2	Oncogene	Oncogene (7) / TsG (1)		Oncogene	Oncogene	TsG	Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
BCL2L1	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
BCL2L11	TsG	TsG (2)			unknown					TsG	TsG			unknown
BCL2L2	Oncogene	Oncogene (1)			unknown									Oncogene
BCL6	Oncogene	Oncogene (8)			Oncogene	Oncogene	Oncogene	Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	unknown
BCOR	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
BCORL1	Oncogene/TsG	Oncogene (2) / TsG (5)			Oncogene, TsG			Oncogene, TsG		TsG	TsG		TsG	unknown
BCR	Oncogene/TsG	Oncogene (5) / TsG (2)			unknown		Oncogene		Oncogene	TsG	Oncogene	Oncogene, TsG	Oncogene	unknown
BIRC3	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG	Oncogene					Oncogene
BLM	TsG	Oncogene (1) / TsG (7)			TsG	TsG	TsG	TsG		TsG	TsG	TsG		Oncogene
BMPR1A	TsG	Oncogene (2) / TsG (7)			Oncogene, TsG		TsG	Oncogene, TsG		TsG	TsG		TsG	TsG
BRAF	Oncogene	Oncogene (8)		Oncogene	Oncogene	Oncogene	Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
BRCA1	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
BRCA2	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
BRD4	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	unknown
BRIP1	TsG	TsG (4)			TsG			TsG			TsG			TsG
BTG1	Oncogene/TsG	Oncogene (1) / TsG (3)			unknown			TsG			TsG	Oncogene	unknown	TsG
BTK	Oncogene/TsG	Oncogene (5) / TsG (3)			Oncogene, TsG			Oncogene, TsG		TsG	Oncogene		Oncogene	Oncogene
C11orf30														
CALR	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene			Oncogene
CARD11	Oncogene	Oncogene (8)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
CASP8	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
CBFB	Oncogene/TsG	Oncogene (2) / TsG (3)			TsG			TsG			TsG	Oncogene	Oncogene	unknown
CBL	Oncogene/TsG	Oncogene (5) / TsG (4)		Oncogene	Oncogene, TsG			Oncogene, TsG		TsG	TsG	Oncogene	Oncogene	unknown
CCND1	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
CCND2	Oncogene	Oncogene (5)			Oncogene		Oncogene	Oncogene			Oncogene		Oncogene	unknown
CCND3	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene			Oncogene		Oncogene	Oncogene
CCNE1	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene			Oncogene
CD274	Oncogene/TsG	Oncogene (2) / TsG (2)			TsG			TsG			Oncogene			Oncogene
CD276					unknown									unknown
CD74	Oncogene	Oncogene (2)			Oncogene			Oncogene						
CD79A	Oncogene	Oncogene (3)			Oncogene			Oncogene			Oncogene			
CD79B	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene		Oncogene	Oncogene
CDC73	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
CDH1	TsG	Oncogene (1) / TsG (8)		TsG	TsG		TsG	TsG	Oncogene	TsG	TsG	TsG	TsG	unknown
CDK12	TsG	TsG (4)			TsG			TsG			TsG		TsG	unknown
CDK4	Oncogene	Oncogene (6)			Oncogene	Oncogene		Oncogene	Oncogene		Oncogene		Oncogene	unknown
CDK6	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene		TsG	Oncogene	Oncogene	TsG	Oncogene			unknown
CDK8	Oncogene	Oncogene (2)			unknown				Oncogene		Oncogene			unknown
CDKN1A	Oncogene/TsG	Oncogene (3) / TsG (6)			Oncogene, TsG			Oncogene, TsG	Oncogene	TsG	TsG	TsG	TsG	unknown
CDKN1B	Oncogene/TsG	Oncogene (2) / TsG (5)			TsG			TsG	Oncogene	TsG	TsG	Oncogene	TsG	unknown
CDKN2A	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
CDKN2B	TsG	TsG (3)			unknown					TsG	TsG	TsG		unknown
CDKN2C	TsG	TsG (8)			TsG		TsG	TsG		TsG	TsG	TsG	TsG	TsG
CEBPA	TsG	TsG (7)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	unknown	unknown
CENPA	Oncogene	Oncogene (1)			unknown									Oncogene
CHD2	TsG	TsG (2)			unknown			TsG					TsG	
CHD4	Oncogene	Oncogene (3)			unknown			Oncogene					Oncogene	Oncogene
CHEK1	TsG	TsG (3)			unknown					TsG	TsG	TsG		unknown
CHEK2	TsG	TsG (8)			TsG		TsG	TsG		TsG	TsG	TsG	TsG	TsG
CIC	TsG	Oncogene (2) / TsG (6)		TsG	Oncogene, TsG			Oncogene, TsG		TsG	TsG		TsG	unknown
CREBBP	TsG	Oncogene (2) / TsG (8)		TsG	Oncogene, TsG		TsG	Oncogene, TsG		TsG	TsG	TsG	TsG	unknown
CRKL	Oncogene	Oncogene (2)			unknown				Oncogene		Oncogene			unknown
CRLF2	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene	Oncogene		
CSF1R	Oncogene	Oncogene (5)		Oncogene	Oncogene			Oncogene				Oncogene		Oncogene
CSF3R	Oncogene	Oncogene (6)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	Oncogene
CSNK1A1	TsG	TsG (2)			unknown					TsG				TsG
CTCF	TsG	TsG (6)			TsG			TsG		TsG	TsG	TsG	TsG	unknown
CTLA4	Oncogene	Oncogene (1)			unknown						Oncogene			
CTNNA1	TsG	TsG (1)			unknown									TsG
CTNNB1	Oncogene	Oncogene (8)		Oncogene	Oncogene		Oncogene	Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	unknown
CUL3	TsG	TsG (4)			unknown			TsG				TsG	TsG	TsG
CUX1	Oncogene/TsG	Oncogene (3) / TsG (5)			Oncogene, TsG			Oncogene, TsG	Oncogene	TsG	TsG		unknown	TsG
CXCR4	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	unknown
CYLD	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
DAXX	Oncogene/TsG	Oncogene (3) / TsG (5)		TsG	Oncogene, TsG			Oncogene, TsG	Oncogene		TsG		TsG	unknown
DCUN1D1	Oncogene	Oncogene (2)			unknown				Oncogene			Oncogene		unknown
DDR2	Oncogene/TsG	Oncogene (4) / TsG (1)			Oncogene			Oncogene		TsG	Oncogene			Oncogene
DDX41	TsG	TsG (2)			unknown						TsG			TsG
DHX15					unknown									unknown
DICER1	TsG	TsG (6)			TsG			TsG		TsG	TsG		TsG	TsG
DIS3	Oncogene/TsG	Oncogene (1) / TsG (2)			unknown				Oncogene		TsG		TsG	unknown
DNAJB1	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown					TsG				Oncogene
DNMT1	Oncogene/TsG	Oncogene (3) / TsG (1)		Oncogene	unknown					TsG	Oncogene	Oncogene		unknown
DNMT3A	Oncogene/TsG	Oncogene (2) / TsG (5)		Oncogene	TsG			TsG		TsG	TsG	Oncogene	TsG	unknown
DNMT3B	TsG	TsG (2)			unknown					TsG	TsG			unknown
DOT1L	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown						Oncogene		TsG	Oncogene
E2F3	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown				Oncogene	TsG	Oncogene			unknown
EED	TsG	TsG (4)			unknown			TsG		TsG	TsG			TsG
EGFL7	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene

EGFR	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
EIF1AX	TsG	TsG (1)			unknown								TsG	
EIF4A2	Oncogene	Oncogene (1)			unknown						Oncogene			
EIF4E	Oncogene	Oncogene (2)			unknown				Oncogene		Oncogene			unknown
EML4	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
EP300	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
EPCAM	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown				Oncogene		TsG			unknown
EPHA3	TsG	TsG (2)			unknown					TsG	TsG		unknown	unknown
EPHA5	TsG	TsG (1)			unknown									TsG
EPHA7	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						Oncogene, TsG		unknown	unknown
EPHB1	TsG	TsG (2)			unknown						TsG			TsG
ERBB2	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
ERBB3	Oncogene	Oncogene (6)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	Oncogene
ERBB4	Oncogene/TsG	Oncogene (4) / TsG (5)			Oncogene, TsG			Oncogene, TsG	Oncogene	TsG	Oncogene	TsG	TsG	unknown
ERCC1					unknown									
ERCC2	Oncogene/TsG	Oncogene (1) / TsG (4)			TsG			TsG			TsG		TsG	Oncogene
ERCC3	Oncogene/TsG	Oncogene (1) / TsG (4)			TsG			TsG			TsG		TsG	Oncogene
ERCC4	TsG	TsG (3)			TsG			TsG			TsG			
ERCC5	TsG	TsG (2)			unknown			TsG			TsG			
ERG	Oncogene	Oncogene (7)			Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	Oncogene
ERRFI1	TsG	TsG (4)			unknown					TsG	TsG	TsG		TsG
ESR1	Oncogene/TsG	Oncogene (4) / TsG (3)			Oncogene, TsG			Oncogene, TsG		TsG	Oncogene		Oncogene	unknown
ETS1	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown							Oncogene, TsG		unknown
ETV1	Oncogene	Oncogene (6)			Oncogene			Oncogene	Oncogene		Oncogene	Oncogene		Oncogene
ETV4	Oncogene	Oncogene (6) / TsG (1)			Oncogene		Oncogene	Oncogene	Oncogene		Oncogene		TsG	Oncogene
ETV5	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene		Oncogene	Oncogene
ETV6	Oncogene/TsG	Oncogene (3) / TsG (5)			TsG		Oncogene	TsG		TsG	TsG	Oncogene, TsG	Oncogene	unknown
EWSR1	Oncogene	Oncogene (7)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
EZH2	Oncogene/TsG	Oncogene (5) / TsG (5)		Oncogene	Oncogene, TsG			Oncogene, TsG		TsG	Oncogene, TsG	Oncogene	TsG	unknown
FAM123B	TsG	TsG (2)		TsG								TsG		
FAM175A	TsG	TsG (1)									TsG			
FAM46C	TsG	TsG (2)									TsG		TsG	
FANCA	TsG	Oncogene (1) / TsG (5)			TsG	TsG		TsG			TsG		TsG	Oncogene
FANCC	TsG	TsG (4)			TsG	TsG		TsG			TsG			
FANCD2	TsG	Oncogene (1) / TsG (5)			TsG	TsG		TsG			TsG		TsG	Oncogene
FANCE	TsG	TsG (3)			TsG	TsG		TsG						
FANCF	TsG	TsG (4)			TsG	TsG		TsG					TsG	
FANCG	TsG	TsG (5)			TsG	TsG		TsG		TsG		TsG		
FANCI	TsG	TsG (1)			unknown	TsG								
FANCL	TsG	TsG (2)			unknown	TsG					TsG			
FAS	Oncogene/TsG	Oncogene (1) / TsG (4)			unknown	Oncogene		TsG		TsG	TsG		TsG	unknown
FAT1	TsG	TsG (5)			unknown			TsG		TsG	TsG	TsG	TsG	unknown
FBXW7	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
FGF1	Oncogene	Oncogene (1)			unknown									Oncogene
FGF10	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
FGF14					unknown									
FGF19	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
FGF2	Oncogene	Oncogene (1)			unknown									Oncogene
FGF23	Oncogene	Oncogene (1)			unknown									Oncogene
FGF3	Oncogene	Oncogene (4)			unknown				Oncogene		Oncogene	Oncogene		Oncogene
FGF4	Oncogene	Oncogene (4)			unknown				Oncogene		Oncogene	Oncogene		Oncogene
FGF5	Oncogene	Oncogene (2)			unknown				Oncogene			Oncogene		unknown
FGF6	Oncogene	Oncogene (2)			unknown				Oncogene			Oncogene		
FGF7	Oncogene	Oncogene (1)			unknown									Oncogene
FGF8	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
FGF9	Oncogene	Oncogene (1)			unknown									Oncogene
FGFR1	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene	Oncogene		Oncogene		Oncogene	unknown
FGFR2	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
FGFR3	Oncogene	Oncogene (8)		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	Oncogene
FGFR4	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	unknown
FH	TsG	TsG (7)			TsG	TsG	TsG	TsG		TsG	TsG	TsG		unknown
FLCN	TsG	TsG (6)			TsG			TsG		TsG	TsG	TsG	TsG	unknown
FLI1	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene	Oncogene		unknown
FLT1	Oncogene	Oncogene (1)			unknown						Oncogene			unknown
FLT3	Oncogene	Oncogene (7) / TsG (2)		Oncogene	Oncogene		TsG	Oncogene		TsG	Oncogene	Oncogene	Oncogene	Oncogene
FLT4	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene		unknown	Oncogene
FOXA1	Oncogene/TsG	Oncogene (4) / TsG (3)			Oncogene			Oncogene	Oncogene	TsG	Oncogene, TsG		TsG	unknown
FOXL2	Oncogene/TsG	Oncogene (6) / TsG (5)		Oncogene	Oncogene, TsG			Oncogene, TsG		TsG	Oncogene, TsG	Oncogene	Oncogene	TsG
FOXO1	Oncogene/TsG	Oncogene (5) / TsG (5)			Oncogene, TsG			Oncogene, TsG	Oncogene	TsG	TsG	Oncogene, TsG	Oncogene	unknown
FOXP1	Oncogene/TsG	Oncogene (3) / TsG (4)			unknown		TsG	Oncogene	Oncogene	TsG	Oncogene, TsG	TsG		unknown
FRS2	Oncogene	Oncogene (1)			unknown									Oncogene
FUBP1	Oncogene/TsG	Oncogene (3) / TsG (3)		TsG	Oncogene			Oncogene	Oncogene		TsG		TsG	unknown
FYN	Oncogene	Oncogene (3)			unknown				Oncogene		Oncogene	Oncogene		unknown
GABRA6					unknown									
GATA1	Oncogene/TsG	Oncogene (5) / TsG (3)		TsG	Oncogene, TsG			Oncogene, TsG	Oncogene				Oncogene	Oncogene
GATA2	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	unknown
GATA3	Oncogene/TsG	Oncogene (3) / TsG (5)		TsG	Oncogene, TsG			Oncogene, TsG			Oncogene, TsG		TsG	unknown
GATA4	TsG	TsG (2)			unknown					TsG				TsG
GATA6	Oncogene	Oncogene (1)			unknown				Oncogene					unknown
GEN1	TsG	TsG (1)			unknown									TsG
GID4					unknown									
GLI1	Oncogene	Oncogene (5) / TsG (1)			Oncogene			Oncogene		TsG	Oncogene	Oncogene	Oncogene	unknown
GNA11	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
GNA13	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown				Oncogene		Oncogene		TsG	
GNAQ	Oncogene	Oncogene (8)		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene	Oncogene	Oncogene	Oncogene
GNAS	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	unknown
GPR124														
GPS2	TsG	TsG (1)			unknown						TsG			
GREM1	Oncogene/TsG	Oncogene (3) / TsG (1)			unknown				Oncogene	TsG	Oncogene			Oncogene
GRIN2A	TsG	Oncogene (1) / TsG (5)			TsG			TsG		TsG	TsG		Oncogene	TsG
GRM3	Oncogene	Oncogene (3)			Oncogene			Oncogene						Oncogene
GSK3B	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown					TsG	Oncogene			Oncogene
H3F3A	Oncogene	Oncogene (5)		Oncogene				Oncogene			Oncogene	Oncogene	Oncogene	
H3F3B	Oncogene	Oncogene (1)						Oncogene						
H3F3C														
HGF	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
HIST1H1C														
HIST1H2BD														
HIST1H3A														
HIST1H3B	Oncogene	Oncogene (4)		Oncogene				Oncogene				Oncogene	Oncogene	
HIST1H3C														
HIST1H3D														
HIST1H3E														
HIST1H3F														
HIST1H3G														
HIST1H3H														
HIST1H3I														
HIST1H3J														
HIST2H3A														
HIST2H3C														
HIST2H3D														
HIST3H3														
HLA-A	TsG	TsG (1)			unknown						TsG		unknown	
HLA-B	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG		unknown	Oncogene
HLA-C	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG			Oncogene

HNF1A	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
HNRNPK					unknown									unknown
HOXB13	Oncogene/TsG	Oncogene (1) / TsG (3)			unknown					TsG	Oncogene, TsG	TsG		unknown
HRAS	Oncogene	Oncogene (8)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
HSD3B1					unknown									
HSP90AA1	Oncogene	Oncogene (2)			unknown								Oncogene	Oncogene
ICOSLG	Oncogene	Oncogene (1)			unknown						Oncogene			
ID3	TsG	TsG (4)			TsG			TsG			TsG		TsG	unknown
IDH1	Oncogene	Oncogene (7) / TsG (3)		Oncogene	Oncogene		TsG	Oncogene	Oncogene	TsG	Oncogene	Oncogene, TsG	Oncogene	unknown
IDH2	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	unknown
IFNGR1	TsG	TsG (2)			unknown						TsG		TsG	
IGF1	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown					TsG	Oncogene			unknown
IGF1R	Oncogene	Oncogene (2)			unknown				Oncogene		Oncogene			unknown
IGF2	Oncogene	Oncogene (2)			unknown				Oncogene		Oncogene			unknown
IKBKE	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
IKZF1	Oncogene/TsG	Oncogene (1) / TsG (3)			TsG			TsG	Oncogene	TsG			unknown	unknown
IL10	Oncogene	Oncogene (1)			unknown									Oncogene
IL7R	Oncogene	Oncogene (6)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	Oncogene
INHA	TsG	TsG (2)			unknown						TsG			TsG
INHBA	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						Oncogene, TsG			unknown
INPP4A					unknown									
INPP4B	TsG	TsG (4)			unknown	TsG				TsG	TsG	TsG		unknown
INSR	Oncogene	Oncogene (1)			unknown						Oncogene			unknown
IRF2	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
IRF4	Oncogene/TsG	Oncogene (5) / TsG (3)			Oncogene, TsG		Oncogene	Oncogene, TsG	Oncogene	TsG	Oncogene		unknown	unknown
IRS1	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
IRS2	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
JAK1	Oncogene/TsG	Oncogene (6) / TsG (3)		Oncogene	Oncogene, TsG			Oncogene, TsG	Oncogene		Oncogene, TsG	Oncogene	unknown	
JAK2	Oncogene	Oncogene (6) / TsG (1)		Oncogene	Oncogene		TsG	Oncogene			Oncogene	Oncogene	unknown	Oncogene
JAK3	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
JUN	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene
KAT6A	Oncogene	Oncogene (4)			Oncogene			Oncogene				Oncogene	unknown	Oncogene
KDM5A	Oncogene/TsG	Oncogene (3) / TsG (1)			Oncogene			Oncogene		TsG	Oncogene			unknown
KDM5C	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
KDM6A	TsG	Oncogene (2) / TsG (6)		TsG	Oncogene, TsG			Oncogene, TsG		TsG	TsG		TsG	unknown
KDR	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene		Oncogene	Oncogene
KEAP1	Oncogene/TsG	Oncogene (1) / TsG (4)			TsG			TsG			TsG		Oncogene	TsG
KEL	Oncogene	Oncogene (1)			unknown								Oncogene	
KIF5B	Oncogene	Oncogene (2)			unknown								Oncogene	Oncogene
KIT	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
KLF4	Oncogene/TsG	Oncogene (6) / TsG (5)		Oncogene	Oncogene, TsG			Oncogene, TsG		TsG	Oncogene, TsG	Oncogene, TsG	Oncogene	unknown
KLHL6	TsG	TsG (1)			unknown								TsG	unknown
KMT2B	TsG	TsG (3)			unknown						TsG		TsG	TsG
KMT2C	TsG	TsG (5)			TsG			TsG		TsG	TsG		TsG	unknown
KMT2D	Oncogene/TsG	Oncogene (2) / TsG (4)			Oncogene, TsG			Oncogene, TsG			TsG		TsG	unknown
KRAS	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
LAMP1					unknown									
LATS1	TsG	TsG (5)			unknown			TsG		TsG	TsG	TsG	TsG	unknown
LATS2	TsG	TsG (5)			unknown			TsG		TsG	TsG	TsG	TsG	unknown
LMO1	Oncogene	Oncogene (6)			Oncogene			Oncogene	Oncogene		Oncogene	Oncogene		Oncogene
LRP1B	TsG	TsG (6)			TsG			TsG		TsG		TsG	TsG	TsG
LYN	Oncogene	Oncogene (3)			unknown						Oncogene	Oncogene		Oncogene
LZTR1	TsG	TsG (5)			TsG			TsG			TsG		TsG	TsG
MAGI2					unknown									
MALT1	Oncogene/TsG	Oncogene (4) / TsG (1)			Oncogene			Oncogene	Oncogene				TsG	Oncogene
MAP2K1	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
MAP2K2	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene			Oncogene
MAP2K4	TsG	Oncogene (2) / TsG (7)			Oncogene, TsG		TsG	Oncogene, TsG		TsG	TsG	TsG	TsG	unknown
MAP3K1	Oncogene/TsG	Oncogene (2) / TsG (5)		TsG	Oncogene, TsG			Oncogene, TsG			TsG		TsG	unknown
MAP3K13	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG			Oncogene			Oncogene
MAP3K14	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
MAP3K4	TsG	TsG (1)			unknown					TsG				
MAPK1	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene		Oncogene	unknown
MAPK3	Oncogene	Oncogene (1)			unknown						Oncogene			
MAX	Oncogene/TsG	Oncogene (1) / TsG (3)			unknown			TsG		TsG	TsG		Oncogene	
MCL1	Oncogene	Oncogene (3)			unknown				Oncogene		Oncogene			Oncogene
MDC1	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown					TsG				Oncogene
MDM2	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
MDM4	Oncogene/TsG	Oncogene (4) / TsG (1)			Oncogene		TsG	Oncogene	Oncogene		Oncogene			unknown
MED12	Oncogene/TsG	Oncogene (4) / TsG (3)		Oncogene	TsG			TsG			Oncogene, TsG	Oncogene	Oncogene	unknown
MEF2B	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown						Oncogene		TsG	Oncogene
MEN1	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
MET	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
MGA	TsG	TsG (3)			unknown						TsG		TsG	TsG
MITF	Oncogene	Oncogene (5) / TsG (1)			Oncogene	Oncogene	Oncogene	Oncogene			Oncogene, TsG			unknown
MLH1	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG		TsG
MLL	Oncogene	Oncogene (2)				Oncogene	Oncogene							
MLLT3	Oncogene	Oncogene (3)			unknown							Oncogene	Oncogene	Oncogene
MPL	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene
MRE11A	Oncogene/TsG	Oncogene (1) / TsG (1)							Oncogene		TsG			
MSH2	TsG	TsG (7)		TsG	TsG		TsG	TsG		TsG	TsG	TsG		unknown
MSH3	TsG	TsG (2)			unknown						TsG			TsG
MSH6	TsG	TsG (4)		TsG	TsG			TsG			TsG			unknown
MST1	TsG	TsG (4)			unknown					TsG	TsG	TsG		TsG
MST1R	Oncogene/TsG	Oncogene (3) / TsG (1)			unknown				Oncogene	TsG	Oncogene			Oncogene
MTOR	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	unknown
MUTYH	TsG	Oncogene (1) / TsG (5)			TsG	TsG		TsG			TsG	TsG		Oncogene
MYB	Oncogene	Oncogene (4)			Oncogene		Oncogene	Oncogene				Oncogene		unknown
MYC	Oncogene	Oncogene (7)			Oncogene	Oncogene	Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
MYCL1	Oncogene	Oncogene (1)					Oncogene							
MYCN	Oncogene	Oncogene (6)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
MYD88	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
MYOD1	Oncogene	Oncogene (1)			unknown			Oncogene						unknown
NAB2	Oncogene/TsG	Oncogene (1) / TsG (2)			TsG			TsG						Oncogene
NBN	TsG	TsG (5)			TsG			TsG		TsG	TsG			TsG
NCOA3	Oncogene	Oncogene (3)			unknown				Oncogene		Oncogene			Oncogene
NCOR1	TsG	TsG (5)		TsG	TsG			TsG			TsG		TsG	unknown
NEGR1					unknown									
NF1	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
NF2	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
NFE2L2	Oncogene	Oncogene (6) / TsG (2)		Oncogene	Oncogene, TsG			Oncogene, TsG			Oncogene	Oncogene	Oncogene	unknown
NFKBIA	TsG	TsG (3)			unknown						TsG		TsG	TsG
NKX2-1	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG	Oncogene		Oncogene		unknown	unknown
NKX3-1	TsG	TsG (3)			unknown					TsG	TsG	TsG		unknown
NOTCH1	Oncogene/TsG	Oncogene (4) / TsG (7)		TsG	Oncogene, TsG		TsG	Oncogene, TsG		TsG	Oncogene, TsG	Oncogene, TsG	unknown	unknown
NOTCH2	Oncogene/TsG	Oncogene (4) / TsG (5)		TsG	Oncogene, TsG			Oncogene, TsG		TsG	Oncogene, TsG	Oncogene	unknown	unknown
NOTCH3	Oncogene/TsG	Oncogene (2) / TsG (2)			unknown					TsG	Oncogene, TsG	Oncogene		unknown
NOTCH4	Oncogene/TsG	Oncogene (2) / TsG (1)			unknown				Oncogene		Oncogene, TsG			unknown
NPM1	Oncogene/TsG	Oncogene (3) / TsG (4)		TsG	Oncogene		TsG	Oncogene		TsG	TsG	Oncogene	unknown	unknown
NRAS	Oncogene	Oncogene (8)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
NRG1	Oncogene/TsG	Oncogene (3) / TsG (2)			TsG			TsG			Oncogene		Oncogene	Oncogene
NSD1	Oncogene/TsG	Oncogene (3) / TsG (1)			unknown						Oncogene, TsG	Oncogene	Oncogene	unknown
NTRK1	Oncogene	Oncogene (6) / TsG (2)			Oncogene, TsG		Oncogene	Oncogene, TsG			Oncogene	Oncogene	Oncogene	unknown
NTRK2	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
NTRK3	Oncogene	Oncogene (5) / TsG (1)			Oncogene			Oncogene	Oncogene	TsG	Oncogene		Oncogene	unknown

NUP93					unknown									
NUTM1	Oncogene	Oncogene (4)			Oncogene			Oncogene	Oncogene					Oncogene
PAK1	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
PAK3					unknown									
PAK7	Oncogene	Oncogene (1)							Oncogene					
PALB2	TsG	TsG (7)			TsG		TsG	TsG		TsG	TsG	TsG		TsG
PARK2	TsG	TsG (3)								TsG	TsG	TsG		
PARP1	TsG	TsG (2)			unknown					TsG	TsG			unknown
PAX3	Oncogene	Oncogene (3)			Oncogene			Oncogene				Oncogene		unknown
PAX5	Oncogene/TsG	Oncogene (3) / TsG (6)		TsG	Oncogene, TsG			Oncogene, TsG		TsG	TsG	Oncogene, TsG		unknown
PAX7	Oncogene	Oncogene (1)			unknown							Oncogene		
PAX8	Oncogene	Oncogene (2)			unknown		Oncogene				Oncogene			unknown
PBRM1	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
PDCD1	Oncogene	Oncogene (1)			unknown						Oncogene			
PDCD1LG2	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene		Oncogene	Oncogene
PDGFRA	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
PDGFRB	Oncogene	Oncogene (6)			Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
PDK1	Oncogene	Oncogene (1)			unknown									Oncogene
PDPK1					unknown									
PGR	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown					TsG	Oncogene			unknown
PHF6	TsG	TsG (8)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	TsG
PHOX2B	TsG	TsG (3)			TsG			TsG			TsG			
PIK3C2B					unknown									
PIK3C2G					unknown									
PIK3C3	TsG	TsG (1)			unknown									TsG
PIK3CA	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
PIK3CB	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene		Oncogene	Oncogene
PIK3CD	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
PIK3CG	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
PIK3R1	TsG	Oncogene (1) / TsG (5)		TsG	TsG			TsG	Oncogene		TsG		TsG	unknown
PIK3R2	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG			Oncogene
PIK3R3	TsG	TsG (2)			unknown						TsG			TsG
PIM1	Oncogene	Oncogene (5) / TsG (1)			Oncogene		Oncogene	Oncogene				Oncogene	TsG	Oncogene
PLCG2	Oncogene	Oncogene (1)			unknown						Oncogene			
PLK2	TsG	TsG (2)			unknown					TsG		TsG		unknown
PMAIP1	TsG	TsG (2)			unknown						TsG			TsG
PMS1	TsG	TsG (2)			unknown						TsG	TsG		
PMS2	TsG	TsG (5)			TsG			TsG			TsG	TsG	TsG	
PNRC1	TsG	TsG (1)			unknown									TsG
POLD1	Oncogene/TsG	Oncogene (1) / TsG (3)			TsG			TsG			TsG		Oncogene	
POLE	TsG	TsG (3)			TsG			TsG			TsG			
PPARG	Oncogene/TsG	Oncogene (2) / TsG (3)			TsG		Oncogene	TsG		TsG	Oncogene			unknown
PPM1D	Oncogene	Oncogene (5) / TsG (1)			Oncogene			Oncogene	Oncogene		Oncogene		TsG	Oncogene
PPP2R1A	Oncogene/TsG	Oncogene (4) / TsG (3)		Oncogene	TsG			TsG			TsG	Oncogene	Oncogene	Oncogene
PPP2R2A	Oncogene	Oncogene (1)			unknown									Oncogene
PPP6C	TsG	TsG (3)			unknown			TsG			TsG		TsG	unknown
PRDM1	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
PREX2	Oncogene	Oncogene (3)			unknown			Oncogene					Oncogene	Oncogene
PRKAR1A	Oncogene/TsG	Oncogene (2) / TsG (5)			Oncogene, TsG			Oncogene, TsG		TsG		TsG	TsG	unknown
PRKCI	Oncogene/TsG	Oncogene (3) / TsG (1)			unknown						Oncogene	Oncogene, TsG		Oncogene
PRKDC					unknown									unknown
PRSS8	TsG	TsG (1)			unknown									TsG
PTCH1	TsG	Oncogene (1) / TsG (7)		TsG	TsG			TsG	Oncogene	TsG	TsG	TsG	TsG	unknown
PTEN	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
PTPN11	Oncogene	Oncogene (7) / TsG (1)		Oncogene	Oncogene		Oncogene	Oncogene		TsG	Oncogene	Oncogene	Oncogene	unknown
PTPRD	TsG	Oncogene (1) / TsG (5)			TsG			TsG		TsG	TsG	TsG	Oncogene	unknown
PTPRS	TsG	TsG (2)			unknown						TsG			TsG
PTPRT	TsG	TsG (5)			TsG			TsG		TsG	TsG		TsG	unknown
QKI	Oncogene/TsG	Oncogene (2) / TsG (4)			Oncogene, TsG			Oncogene, TsG					TsG	TsG
RAB35	Oncogene	Oncogene (1)			unknown						Oncogene			
RAC1	Oncogene	Oncogene (5)			Oncogene			Oncogene	Oncogene		Oncogene		Oncogene	unknown
RAD21	Oncogene/TsG	Oncogene (3) / TsG (4)			Oncogene, TsG			Oncogene, TsG			TsG		TsG	Oncogene
RAD50	TsG	TsG (2)			unknown						TsG			TsG
RAD51	TsG	TsG (1)			unknown						TsG			unknown
RAD51B	TsG	TsG (4)			TsG			TsG			TsG			TsG
RAD51C	TsG	TsG (4)			unknown					TsG	TsG	TsG		TsG
RAD51D	TsG	TsG (1)			unknown						TsG			
RAD52					unknown									
RAD54L					unknown									
RAF1	Oncogene	Oncogene (7)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
RANBP2	TsG	TsG (3)			TsG			TsG					TsG	unknown
RARA	Oncogene	Oncogene (3)			Oncogene			Oncogene				Oncogene		unknown
RASA1	Oncogene/TsG	Oncogene (1) / TsG (3)			unknown						TsG	Oncogene	TsG	TsG
RB1	TsG	Oncogene (1) / TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	Oncogene, TsG	TsG	unknown
RBM10	TsG	TsG (3)			unknown			TsG			TsG		TsG	unknown
RECQL4	Oncogene/TsG	Oncogene (2) / TsG (5)			Oncogene, TsG	TsG		Oncogene, TsG			TsG		TsG	unknown
REL	Oncogene	Oncogene (5)			unknown		Oncogene	Oncogene			Oncogene	Oncogene		Oncogene
RET	Oncogene	Oncogene (7)		Oncogene	Oncogene		Oncogene	Oncogene			Oncogene	Oncogene	Oncogene	unknown
RFWD2	Oncogene/TsG	Oncogene (1) / TsG (1)								TsG	Oncogene			
RHEB	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
RHOA	Oncogene/TsG	Oncogene (5) / TsG (4)			Oncogene, TsG			Oncogene, TsG		TsG	Oncogene	Oncogene, TsG	Oncogene	unknown
RICTOR	Oncogene	Oncogene (2)			unknown						Oncogene			Oncogene
RIT1	Oncogene	Oncogene (1)			unknown						Oncogene			unknown
RNF43	TsG	Oncogene (1) / TsG (5)		TsG	TsG			TsG	Oncogene		TsG		TsG	unknown
ROS1	Oncogene	Oncogene (5)			Oncogene		Oncogene	Oncogene			Oncogene	Oncogene		unknown
RPS6KA4	Oncogene	Oncogene (1)			unknown						Oncogene			
RPS6KB1	Oncogene	Oncogene (1)			unknown									Oncogene
RPS6KB2	Oncogene	Oncogene (1)			unknown						Oncogene			
RPTOR	Oncogene	Oncogene (1)			unknown						Oncogene			
RUNX1	Oncogene/TsG	Oncogene (3) / TsG (6)		TsG	Oncogene, TsG		TsG	Oncogene, TsG		TsG	TsG	Oncogene	unknown	unknown
RUNX1T1	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG			Oncogene	Oncogene	unknown	unknown
RYBP	TsG	TsG (1)			unknown						TsG			unknown
SDHA	TsG	TsG (6)			TsG			TsG		TsG	TsG	TsG		TsG
SDHAF2	TsG	TsG (2)						TsG			TsG			
SDHB	TsG	TsG (7)			TsG		TsG	TsG		TsG	TsG	TsG		TsG
SDHC	TsG	TsG (4)			TsG			TsG			TsG			TsG
SDHD	TsG	TsG (7)			TsG		TsG	TsG		TsG	TsG	TsG		TsG
SETBP1	Oncogene	Oncogene (7)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	Oncogene
SETD2	TsG	TsG (6)		TsG	TsG			TsG		TsG	TsG		TsG	unknown
SF3B1	Oncogene	Oncogene (6) / TsG (1)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	TsG
SH2B3	TsG	TsG (4)			TsG			TsG		TsG	TsG			unknown
SH2D1A	TsG	TsG (1)			unknown						TsG			
SHQ1	TsG	TsG (2)			unknown					TsG	TsG			
SLIT2	TsG	TsG (2)			unknown					TsG		TsG		unknown
SLX4	TsG	TsG (2)			unknown					TsG	TsG			
SMAD2	TsG	TsG (7)		TsG	TsG			TsG		TsG	TsG	TsG	TsG	unknown
SMAD3	TsG	TsG (5)			TsG			TsG			TsG	TsG	TsG	unknown
SMAD4	TsG	TsG (8)		TsG	TsG	TsG		TsG		TsG	TsG	TsG	TsG	unknown
SMARCA4	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
SMARCB1	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
SMARCD1	TsG	TsG (1)			unknown			TsG					unknown	
SMC1A	Oncogene/TsG	Oncogene (2) / TsG (2)			unknown			TsG			TsG		Oncogene	Oncogene
SMC3	TsG	TsG (1)			unknown						TsG			
SMO	Oncogene	Oncogene (9) / TsG (1)		Oncogene	Oncogene	Oncogene	Oncogene	Oncogene			Oncogene	Oncogene, TsG	Oncogene	Oncogene
SNCAIP					unknown									

SOCS1	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
SOX10					unknown									unknown
SOX17	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG		Oncogene	unknown
SOX2	Oncogene	Oncogene (2)			unknown			Oncogene			Oncogene			unknown
SOX9	Oncogene/TsG	Oncogene (1) / TsG (3)		TsG	unknown						Oncogene, TsG		TsG	unknown
SPEN	TsG	TsG (3)			unknown			TsG			TsG		unknown	TsG
SPOP	Oncogene/TsG	Oncogene (3) / TsG (4)		Oncogene	TsG			TsG		TsG	TsG	Oncogene	Oncogene	unknown
SPTA1					unknown									
SRC	Oncogene	Oncogene (5)			Oncogene			Oncogene			Oncogene	Oncogene		Oncogene
SRSF2	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene				Oncogene	Oncogene	Oncogene
STAG1	TsG	TsG (2)			unknown			TsG			TsG			
STAG2	TsG	TsG (6)		TsG	TsG			TsG			TsG		TsG	TsG
STAT3	Oncogene/TsG	Oncogene (3) / TsG (1)			Oncogene			Oncogene		TsG	Oncogene		unknown	unknown
STAT4					unknown									
STAT5A	Oncogene/TsG	Oncogene (1) / TsG (2)			unknown					TsG	Oncogene	TsG		unknown
STAT5B	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG			Oncogene		unknown	Oncogene
STK11	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
STK40					unknown									
SUFU	TsG	TsG (7)			TsG		TsG	TsG		TsG	TsG	TsG		TsG
SUZ12	Oncogene/TsG	Oncogene (3) / TsG (4)			unknown		TsG	Oncogene, TsG		TsG	TsG	Oncogene	Oncogene	unknown
SYK	Oncogene/TsG	Oncogene (3) / TsG (3)			Oncogene		TsG	Oncogene		TsG	Oncogene	TsG		unknown
TAF1	Oncogene	Oncogene (1)			unknown				Oncogene					
TBX3	Oncogene/TsG	Oncogene (3) / TsG (4)			Oncogene, TsG			Oncogene, TsG	Oncogene		TsG		TsG	unknown
TCEB1														
TCF3	Oncogene/TsG	Oncogene (3) / TsG (5)			Oncogene, TsG		TsG	Oncogene, TsG		TsG	TsG	Oncogene		unknown
TCF7L2	Oncogene/TsG	Oncogene (4) / TsG (3)			Oncogene			Oncogene		TsG	TsG	TsG	Oncogene	Oncogene
TERC					unknown									
TERT	Oncogene/TsG	Oncogene (4) / TsG (2)			Oncogene, TsG			Oncogene, TsG			Oncogene			Oncogene
TET1	Oncogene/TsG	Oncogene (1) / TsG (2)			unknown			Oncogene, TsG			TsG		unknown	unknown
TET2	TsG	Oncogene (1) / TsG (7)		TsG	TsG		Oncogene	TsG		TsG	TsG	TsG	TsG	unknown
TFE3	Oncogene	Oncogene (5) / TsG (1)			Oncogene			Oncogene			Oncogene	Oncogene, TsG		Oncogene
TFRC					unknown									
TGFBR1	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						TsG			Oncogene
TGFBR2	TsG	TsG (7)			TsG			TsG		TsG	TsG	TsG	TsG	TsG
TMEM127	TsG	TsG (5)			unknown			TsG		TsG	TsG	TsG		TsG
TMPRSS2	Oncogene	Oncogene (2)			unknown				Oncogene					Oncogene
TNFAIP3	TsG	TsG (8)		TsG	TsG		TsG	TsG		TsG	TsG	TsG	TsG	unknown
TNFRSF14	TsG	TsG (3)			unknown			TsG			TsG		TsG	unknown
TOP1	Oncogene/TsG	Oncogene (2) / TsG (2)			unknown						TsG	Oncogene	TsG	Oncogene
TOP2A	Oncogene	Oncogene (1)			unknown									Oncogene
TP53	TsG	Oncogene (2) / TsG (9)		TsG	Oncogene, TsG	TsG	TsG	Oncogene, TsG		TsG	TsG	TsG	TsG	unknown
TP63	Oncogene/TsG	Oncogene (3) / TsG (5)			Oncogene, TsG			Oncogene, TsG		TsG	Oncogene, TsG	TsG	unknown	unknown
TRAF2	Oncogene	Oncogene (1)			unknown									Oncogene
TRAF7	TsG	TsG (3)		TsG	TsG			TsG						
TSC1	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
TSC2	TsG	TsG (8)			TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
TSHR	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene		Oncogene
U2AF1	Oncogene	Oncogene (6)		Oncogene	Oncogene			Oncogene			Oncogene	Oncogene	Oncogene	
VEGFA	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown					TsG	Oncogene			unknown
VHL	TsG	TsG (9)		TsG	TsG	TsG	TsG	TsG		TsG	TsG	TsG	TsG	unknown
VTCN1	TsG	TsG (1)			unknown									TsG
WISP3	TsG	TsG (2)								TsG		TsG		
WT1	TsG	Oncogene (4) / TsG (9)		TsG	Oncogene, TsG	TsG	TsG	Oncogene, TsG		TsG	Oncogene, TsG	Oncogene, TsG	TsG	unknown
XIAP	Oncogene/TsG	Oncogene (1) / TsG (1)			unknown						Oncogene			TsG
XPO1	Oncogene	Oncogene (4)			Oncogene			Oncogene			Oncogene		Oncogene	unknown
XRCC2	TsG	TsG (1)			unknown						TsG			
YAP1	Oncogene/TsG	Oncogene (2) / TsG (2)			unknown					TsG	Oncogene	Oncogene, TsG		unknown
YES1	Oncogene	Oncogene (3)			unknown						Oncogene	Oncogene		Oncogene
ZBTB2	Oncogene	Oncogene (1)			unknown									Oncogene
ZBTB7A					unknown									unknown
ZFHX3	TsG	TsG (5)			unknown			TsG		TsG	TsG	TsG	TsG	unknown
ZNF217					unknown									unknown
ZNF703	Oncogene	Oncogene (1)			unknown									Oncogene
ZRSR2	TsG	TsG (2)			TsG			TsG						

Annex 4: Common fusion gene list (v1) *(not yet complete)*

Common fusion gene list in solid and hematological tumors v1

Fusion gene	Gene A	Gene B	Transcript ID A	Transcript ID B	Exon A	Exon B	Breakpoint A	Breakpoint B	remark	Found in
ADCY9-PRKCB	ADCY9	PRKCB								Lung
AFAP1-NTRK2	AFAP1	NTRK2		NM_006180.3						Glioma
AGBL4-NTRK2	AGBL4	NTRK2		NM_006180.3						Glioma
AGGF1-RAF1	AGGF1	RAF1		NM_002880.3						Prostate
AGGF1-RAF1	AGGF1	RAF1		NM_002880.3						Prostate
AGK-BRAF	AGK	BRAF		NM_004333.4						Skin; thyroid
AKAP13-RET	AKAP13	RET		NM_020975.4						Thyroid
ANK1-FGFR1	ANK1	FGFR1		NM_023110.2						Breast
ANXA4-PKN1	ANXA4	PKN1								Liver
AP3B1-BRAF	AP3B1	BRAF		NM_004333.4						Thyroid
ARHGEF18-INSR	ARHGEF18	INSR		NM_000208.2						Ovarian
ARHGEF2-NTRK1	ARHGEF2	NTRK1		NM_002529.3						Glioblastoma
ATG7-BRAF	ATG7	BRAF		NM_004333.4						Skin
AXL-MBIP	AXL	MBIP	NM_021913.4							
BAG4-FGFR1	BAG4	FGFR1		NM_023110.2						Lung
BAIAP2L1-MET	BAIAP2L1	MET		NM_001127500.1						Kidney
BCAN-NTRK1	BCAN	NTRK1		NM_002529.3						Glioblastoma
BCL2L11-BRAF	BCL2L11	BRAF		NM_004333.4						Thyroid
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	1	2	chr22:23524426	chr9:133729451	minor e1-a2	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	13	2	chr22:23631808	chr9:133729451	major b2-a2	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	14	2	chr22:23632600	chr9:133729451	major b3-a2	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	1	3			minor e1-a3	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	13	3			major b2-a3	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	14	3			major b3-a3	CML/ALL
BCR-ABL1	BCR	ABL1	NM_004327.3	NM_005157.6	19	2			micro e19-a2	CML/ALL
BRCA2-SLC7A1	BRCA2	SLC7A1	NM_000059.3	NM_003045	3' AA93	8	chr13:32893426	chr13:30096454		
BTB1-NTRK3	BTB1	NTRK3		NM_002530.4						Glioma
C8ORF34-MET	C8ORF34	MET		NM_001127500.1						Kidney
CAMK2D-ANK2	CAMK2D	ANK2								Glioma; lung
CASZ1-MTOR	CASZ1	MTOR		NM_004958.3						Stomach
CBFA2T3-GLIS2	CBFA2T3	GLIS2								Leukemia
CBFB-MYH11	CBFB	MYH11	NM_022845.2	NM_002474.3	5	33	chr16:67116211	chr16:15814908	typeA	Leukemia
CBFB-MYH11	CBFB	MYH11	NM_022845.2	NM_002474.3	5	29			typeD	Leukemia
CBFB-MYH11	CBFB	MYH11	NM_022845.2	NM_002474.3	5	28			typeE	Leukemia
CCDC6-RET	CCDC6	RET		NM_020975.4						Thyroid; lung; colon
CCDC6-ROS1	CCDC6	ROS1		NM_002944.2						Lung
CD74-NRG1	CD74	NRG1	NM_001025159.2	NM_013956.3						Lung
CD74-NTRK1	CD74	NTRK1	NM_001025159.2	NM_002529.3						Lung
CD74-ROS1	CD74	ROS1	NM_001025159.2	NM_002944.2	6	34	chr5:149784243	chr6:117645578		Lung
CD74-ROS1	CD74	ROS1	NM_001025159.2	NM_002944.2						Lung
CDC27-BRAF	CDC27	BRAF		NM_004333.4						Skin
CEP85L-ROS1	CEP85L	ROS1		NM_002944.2						Glioblastoma
CHTOP-NTRK1	CHTOP	NTRK1		NM_002529.3						Glioblastoma
CLCN6-RAF1	CLCN6	RAF1		NM_002880.3						Skin
CLTC-ROS1	CLTC	ROS1		NM_002944.2						Lung
CPD-ERBB2	CPD	ERBB2		NM_004448.2						Stomach
CUX1-RET	CUX1	RET		NM_020975.4						
DDR1-PAK1	DDR1	PAK1		NM_002576.5						Ovarian
DDX42-RPS6KB1	DDX42	RPS6KB1		NM_003161.3						Breast
DEK-NUP214	DEK	NUP214								Leukemia
DSCR4-ERG	DSCR4	ERG		NM_001136154.1	2	8	chr21:39492401	chr21:39764366		
EFNA3-PIK3C2G	EFNA3	PIK3C2G		NM_004570.4						Breast
EGFR-EGFR*	EGFR	EGFR	NM_005228.3	NM_005228.3	1	8	chr7:55087058	chr7:55223523		Lung
EGFR-SEPT14	EGFR	SEPT14	NM_005228.3	NM_207366	24	10	chr7:55268106	chr7:55863785		Glioblastoma
EML4-ALK	EML4	ALK	NM_019063.3	NM_004304.4	13	20	chr2:42522656	chr2:29446394	var1	Lung; thyroid
EML4-ALK	EML4	ALK	NM_019063.3	NM_004304.4	20	20	chr2:42552694	chr2:29446394	var2	Lung; thyroid
EML4-ALK	EML4	ALK	NM_019063.3	NM_004304.4	6	20	chr2:42491871	chr2:29446394	var3a	Lung; thyroid
EML4-ALK	EML4	ALK	NM_019063.3	NM_004304.4	6'	20	chr2:	chr2:29446394	var3b	Lung; thyroid
EML4-NTRK3	EML4	NTRK3	NM_019063.3	NM_002530.4						many
ERBB2-PPP1R1B	ERBB2	PPP1R1B	NM_004448.2							Liver
ERC1-PIK3C2G	ERC1	PIK3C2G		NM_004570.4						Breast
ERC1-RET	ERC1	RET		NM_020975.4						Thyroid ; breast
ERLIN2-FGFR1	ERLIN2	FGFR1		NM_023110.2						Breast
ETV6-ABL1	ETV6	ABL1	NM_001987.4	NM_005157.6	4	2	chr12:12006495	chr9:133729451		Leukemia
ETV6-ABL1	ETV6	ABL1	NM_001987.4	NM_005157.6	5	2	chr12:12022903	chr9:133729451		Leukemia
ETV6-MN1	ETV6	MN1	NM_001987.4							Leukemia
ETV6-NTRK3	ETV6	NTRK3	NM_001987.4	NM_002530.4	5	15	chr12:12022903	chr15:88483984		many
ETV6-NTRK3	ETV6	NTRK3	NM_001987.4	NM_002530.4						Skin; breast; colon; thyroid
ETV6-PDGFRB	ETV6	PDGFRB	NM_001987.4	NM_002609.3						Leukemia
ETV6-RUNX1	ETV6	RUNX1	NM_001987.4	NM_001754.4						Leukemia
EZR-ERBB4	EZR	ERBB4		NM_005235.2						Lung
EZR-ROS1	EZR	ROS1		NM_002944.2						Lung
FAM114A2-BRAF	FAM114A2	BRAF		NM_004333.4						Thyroid
FGFR2-CASP7	FGFR2	CASP7	NM_022970.3							Breast
FGFR2-CCAR2	FGFR2	CCAR2	NM_022970.3							Lung
FGFR2-CCDC6	FGFR2	CCDC6	NM_022970.3							Breast
FGFR2-TACC2	FGFR2	TACC2	NM_022970.3							Stomach
FGFR3-AES	FGFR3	AES	NM_001163213.1							Prostate
FGFR3-BAIAP2L1	FGFR3	BAIAP2L1	NM_001163213.1	NM_018842	17	2	chr4:1808661	chr7:97991744		
FGFR3-ELAVL3	FGFR3	ELAVL3	NM_001163213.1							Glioma
FGFR3-TACC3	FGFR3	TACC3	NM_001163213.1							
FGFR3-TACC3	FGFR3	TACC3	NM_001163213.1	NM_006342	17	11	chr4:1808661	chr4:1741429		
FGFR3-TACC3	FGFR3	TACC3	NM_001163213.1							many
FIP1L1-PDGFRA	FIP1L1	PDGFRA		NM_006206.4	11	12	chr4:54280889	chr4:55141053		Leukemia
FKBP15-RET	FKBP15	RET		NM_020975.4						Thyroid
FNDC3B-PIK3CA	FNDC3B	PIK3CA		NM_006218.2						Uterine
FUS-ERG	FUS	ERG		NM_001136154.1						Leukemia
GGA2-PRKCB	GGA2	PRKCB								Glioma
GOPC-ROS1	GOPC	ROS1		NM_002944.2						Lung

GTF2IRD1-ALK	GTF2IRD1	ALK		NM_004304.4						Thyroid
HIP1-ALK	HIP1	ALK	NM_005338	NM_004304.4	21	20	chr7:75183412	chr2:29446394		Lung
IGF2BP3-PRKCA	IGF2BP3	PRKCA								Lung
IRF2BP2-NTRK1	IRF2BP2	NTRK1		NM_002529.3						Thyroid
KAT6A-CREBBP	KAT6A	CREBBP	NM_006766.3	NM_004380.2	17	2	chr8:41794774	chr16:3901010		Leukemia
KAZN-MTOR	KAZN	MTOR		NM_004958.3						Uterine
KDM7A-BRAF	KDM7A	BRAF		NM_004333.4						Prostate
KIF5B-MET	KIF5B	MET	NM_004521.2	NM_001127500.1						Lung
KIF5B-RET	KIF5B	RET	NM_004521.2	NM_020975.4	24	11	chr10:32306071	chr10:43609928		Lung; thyroid
KIF5B-RET	KIF5B	RET	NM_004521.2	NM_020975.4	15	12	chr10:32317356	chr10:43612032		Lung; thyroid
KIT-PDGFRA	KIT	PDGFRA	NM_000222.2	NM_006206.4						Breast
KMT2A-AFDN	KMT2A	AFDN	NM_001197104.1							Leukemia
KMT2A-AFF1	KMT2A	AFF1	NM_001197104.1							Leukemia
KMT2A-ELL	KMT2A	ELL	NM_001197104.1							Leukemia
KMT2A-EPS15	KMT2A	EPS15	NM_001197104.1							Leukemia
KMT2A-FOXO4	KMT2A	FOXO4	NM_001197104.1							Leukemia
KMT2A-MLLT1	KMT2A	MLLT1	NM_001197104.1							Leukemia
KMT2A-MLLT10	KMT2A	MLLT10	NM_001197104.1							Leukemia
KMT2A-MLLT11	KMT2A	MLLT11	NM_001197104.1							Leukemia
KMT2A-MLLT3	KMT2A	MLLT3	NM_001197104.1	NM_004529.2						Leukemia
KMT2A-MLLT4	KMT2A	MLLT4	NM_001197104.1							Leukemia
KMT2A-MLLT6	KMT2A	MLLT6	NM_001197104.1							Leukemia
LMNA-NTRK1	LMNA	NTRK1	NM_005572.3	NM_002529.3	2	11	chr1:156100564	chr1:156844698		
LMNA-RAF1	LMNA	RAF1	NM_005572.3	NM_002880.3						Skin
LRIG3-ROS1	LRIG3	ROS1		NM_002944.2						Lung
LYN-NTRK3	LYN	NTRK3		NM_002530.4						Head and Neck
MACF1-BRAF	MACF1	BRAF		NM_004333.4						Thyroid
MAP2K2-INSR	MAP2K2	INSR	NM_030662.3	NM_000208.2						Ovarian
MET-MET*	MET	MET	NM_001127500.1	NM_001127500.1	13	15	chr7:116411708	chr7:116414935		Lung
MKRN1-BRAF	MKRN1	BRAF		NM_004333.4						Thyroid
MPRIP-NTRK1	MPRIP	NTRK1		NM_002529.3						Lung
MPRIP-RAF1	MPRIP	RAF1		NM_002880.3						Skin
MTSS1-ERBB2	MTSS1	ERBB2		NM_004448.2						Bladder
NACC2-NTRK2	NACC2	NTRK2		NM_006180.3						Astrocytoma
NAP1L1-STK38L	NAP1L1	STK38L								Breast
NARS2-PAK1	NARS2	PAK1		NM_002576.5						Skin
NCOA4-RET	NCOA4	RET	NM_005437	NM_020975.4	7	12	chr10:51582939	chr10:43612032		Thyroid
NFASC-NTRK1	NFASC	NTRK1		NM_002529.3						Glioblastoma
NPM1-ALK	NPM1	ALK	NM_002520.6	NM_004304.4						Lymphoma
NPM1-MLF1	NPM1	MLF1	NM_002520.6							Leukemia
NPM1-RARA	NPM1	RARA	NM_002520.6	NM_000964.3						Leukemia
NUP98-KDM5A	NUP98	KDM5A								Leukemia
NUP98-NSD1	NUP98	NSD1		NM_022455.4						Leukemia
OXR1-MET	OXR1	MET		NM_001127500.1						Liver
PAN3-NTRK2	PAN3	NTRK2		NM_006180.3						Head and Neck
PAPD7-RAF1	PAPD7	RAF1		NM_002880.3						Prostate
PAX8-PPARG	PAX8	PPARG	NM_003466.3	NM_015869.4	9	2	chr2:113992971	chr3:12421203		
PCM1-JAK2	PCM1	JAK2		NM_004972.3	23	12	chr8:17830196	chr9:5069925		Leukemia
PDGFRA-FIP1L1	PDGFRA	FIP1L1	NM_006206.4							Glioma
PML-RARA	PML	RARA	NM_033238	NM_000964.3	6'	intron2	chr15:74325744	chr17:38499690	bcr1	Leukemia
PML-RARA	PML	RARA	NM_033238	NM_000964.3	6	3	chr15:74325755	chr17:38504568	bcr1	Leukemia
PML-RARA	PML	RARA	NM_033238	NM_000964.3	6'	3	?	?	bcr2	Leukemia
PML-RARA	PML	RARA	NM_033238	NM_000964.3	3	3	chr15:74315749	chr17:38504568	bcr3	Leukemia
PPL-NTRK1	PPL	NTRK1		NM_002529.3						Thyroid
PTAR1-PIP5K1B	PTAR1	PIP5K1B								Sarcoma
PTPRZ1-MET	PTPRZ1	MET		NM_001127500.1						Glioma
PVT1-MYC	PVT1	MYC	NR_003367	NM_002467.4	1	2	chr8:128806980	chr8:128750494		
QKI-NTRK2	QKI	NTRK2		NM_006180.3						Astrocytoma
R3HDM2-PIP4K2C	R3HDM2	PIP4K2C								Glioblastoma
RAB3B-PKN2	RAB3B	PKN2								Sarcoma
RAF1-AGGF1	RAF1	AGGF1	NM_002880.3							Thyroid
RAF1-AGGF1	RAF1	AGGF1	NM_002880.3							Thyroid
RBM15-MKL1	RBM15	MKL1								Leukemia
RBPMS-NTRK3	RBPMS	NTRK3		NM_002530.4						Thyroid
RELCH-RET	RELCH	RET		NM_020975.4						
RHOT1-FGFR1	RHOT1	FGFR1		NM_023110.2						Breast
RIMKLB-PIP4K2A	RIMKLB	PIP4K2A								Glioma
RPS6KB1-VMP1	RPS6KB1	VMP1	NM_003161.3	NM_030938	1	11	chr17:57970686	chr17:57915655	out-of-frame?	
RUNX1-MECOM	RUNX1	MECOM	NM_001754.4							Leukemia
RUNX1-RUNX1T1	RUNX1	RUNX1T1	NM_001754.4		3	3	chr21:36231771	chr8:93029591		Leukemia
SCAF11-PDGFRA	SCAF11	PDGFRA		NM_006206.4						Lung
SDC4-ROS1	SDC4	ROS1		NM_002944.2	4	32	chr20:43959006	chr6:117650609		Lung
SET-NUP214	SET	NUP214								Leukemia
SLC34A2-ROS1	SLC34A2	ROS1		NM_002944.2	4	34	chr4:25665952	chr6:117645578		Lung
SLC34A2-ROS1	SLC34A2	ROS1		NM_002944.2	13'AA674	32	chr4:25678323	chr6:117650609		Lung
SLC3A2-NRG1	SLC3A2	NRG1		NM_013956.3						Lung
SLC45A3-BRAF	SLC45A3	BRAF		NM_004333.4	1	8	chr1:205649522	chr7:140494267		
SLC45A3-ERG	SLC45A3	ERG		NM_001136154.1	1	4	chr1:205649522	chr21:39817544		
SLC45A3-ETV1	SLC45A3	ETV1		NM_004956.4	1	7	chr1:205649522	chr7:13978871		
SMEK2-ALK	SMEK2	ALK		NM_004304.4						Rectum
SND1-BRAF	SND1	BRAF		NM_004333.4						Thyroid
SPECC1L-RET	SPECC1L	RET		NM_020975.4						Thyroid
SPINT2-PAK1	SPINT2	PAK1		NM_002576.5						Breast
SPNS1-PRKCB	SPNS1	PRKCB								Lung
SQSTM1-NTRK1	SQSTM1	NTRK1		NM_002529.3						Thyroid
SQSTM1-NTRK2	SQSTM1	NTRK2		NM_006180.3						Glioma
SRI-PIP4K2C	SRI	PIP4K2C								Sarcoma
SSBP2-NTRK1	SSBP2	NTRK1		NM_002529.3						Thyroid
STARD3-STRADA	STARD3	STRADA								Breast
STIL-TAL1	STIL	TAL1								Leukemia
STK24-PIP5K1B	STK24	PIP5K1B								Breast
STRN-ALK	STRN	ALK		NM_004304.4						Thyroid; kidney
TANC2-PRKCA	TANC2	PRKCA								Lung
TAX1BP1-BRAF	TAX1BP1	BRAF		NM_004333.4						Skin
TBL1XR1-PIK3CA	TBL1XR1	PIK3CA		NM_006218.2						Prostate; breast

TBL1XR1-RET	TBL1XR1	RET		NM_020975.4						Thyroid
TCF3-HLF	TCF3	HLF	NM_003200.3							Leukemia
TCF3-PBX1	TCF3	PBX1	NM_003200.3		16	3	chr19:1619110	chr1:164761731		Leukemia
TECR-PKN1	TECR	PKN1								Uterine
TECR-PKN1	TECR	PKN1								Lung
TFG-MET	TFG	MET		NM_001127500.1						Thyroid
TFG-NTRK1	TFG	NTRK1		NM_002529.3						Thyroid
TMEM165-PDGFRA	TMEM165	PDGFRA		NM_006206.4						Glioblastoma
TMPRSS2-ERG	TMPRSS2	ERG	NM_005656.4	NM_001136154.1	1	2	chr21:42880008	chr21:39956869		Prostate
TMPRSS2-ERG	TMPRSS2	ERG	NM_005656.4	NM_001136154.1	1	4	chr21:42880008	chr21:39817544		Prostate
TMPRSS2-ERG	TMPRSS2	ERG	NM_005656.4	NM_001136154.1	1'	4	chr21:42879876	chr21:39817544		Prostate
TP53-NTRK1	TP53	NTRK1	NM_000546.5	NM_002529.3						Skin
TPM1-ALK	TPM1	ALK		NM_004304.4						Bladder
TPM3-NTRK1	TPM3	NTRK1	NM_001043353.2	NM_002529.3	7	10	chr1:154142876	chr1:156844363		many
TPM3-NTRK1	TPM3	NTRK1	NM_001043353.2	NM_002529.3						Sarcoma; thyroid
TPM3-ROS1	TPM3	ROS1	NM_001043353.2	NM_002944.2						Lung
TPR-NTRK1	TPR	NTRK1		NM_002529.3						Thyroid
TRAK1-RAF1	TRAK1	RAF1		NM_002880.3						Skin
TRIM24-BRAF	TRIM24	BRAF		NM_004333.4						Rectum
TRIM24-NTRK2	TRIM24	NTRK2		NM_006180.3						Lung
TRIM27-RET	TRIM27	RET		NM_020975.4						Thyroid
TRIM33-RET	TRIM33	RET		NM_020975.4						Lung
TRIO-TERT	TRIO	TERT								Sarcoma
TUBD1-RPS6KB1	TUBD1	RPS6KB1		NM_003161.3						Lung
TUFT1-PKN2	TUFT1	PKN2								Sarcoma
VCL-NTRK2	VCL	NTRK2		NM_006180.3						Glioma
WASF2-FGR	WASF2	FGR								Skin; ovarian; lung
WHSC1L1-FGFR1	WHSC1L1	FGFR1		NM_023110.2						Breast
WNK1-STK38L	WNK1	STK38L								Glioma
XRN1-PIP4K2A	XRN1	PIP4K2A								Breast
ZBTB16-RARA	ZBTB16	RARA		NM_000964.3						Leukemia
ZC3HAV1-BRAF	ZC3HAV1	BRAF		NM_004333.4						Thyroid
ZNF37A-PIP5K1B	ZNF37A	PIP5K1B								Breast
ZNF577-FGFR1	ZNF577	FGFR1		NM_023110.2						Breast
ZNF791-FGFR1	ZNF791	FGFR1		NM_023110.2						Breast

* exon skipping event