



# **Cancer Molecular Diagnostics Solid Tumour Service Users' Guide**

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## Laboratory Contact Details

### General Enquiries

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### Laboratory

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- Senior Medical Scientist
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- Senior Medical Scientist
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## Sample selection and dispatch

All samples should be submitted as FFPE blocks with an accompanying H&E slide. The H&E stained slide must be representative of the material in the block so a recent H&E is advised. The slide will be held in the CMD laboratory in case the result needs to be queried in the future, for this reason a slide cut specifically for molecular testing is advised.

## Reporting of results

Results are reported in print and by email where requested. Reports can be sent to two recipients by standard mail or multiple recipients by email. In many cases it is common practice to add the treating clinician or practice nurse to the email list to ensure that the result arrives to the clinic as rapidly as possible. Results will not be emailed by default, the email addresses must be specified in the recipients section of the test request form.

## Funding

The National Cancer Control Program currently supports the cost of mutation testing for predictive mutations in lung adenocarcinoma, colorectal adenocarcinoma and malignant melanoma for patients in public hospitals. The cost of testing for private hospitals is not covered under the scope of this funding so testing must be provided under an up to date service level agreement.

Funding is currently provided by Novartis to support the cost of GIST mutation testing in St James's Hospital and the maintenance of the associated national GIST registry.

Tests marked as 'Research Use Only' are not currently covered by NCCP or pharmaceutical company funding and must be paid for by the referring laboratory.

## Lung Mutation Panel

The lung mutation panel is focussed on the assessment of treatment guiding *EGFR* mutations and *ALK* translocations. In addition to the standard of care assays a number of research use only assays are available singly or as a component of a larger research panel\*.

**Sample requirement:** FFPE block

**Tumour cellularity requirement:** >10% tumour cell content (ideally >30%)

**Tumour type:** Primary or metastatic lesion

**Average turn around time:** 7 working days

**Maximum turn around time:** 10 working days

### EGFR

Mutations of the *EGFR* gene have been associated with an increased likelihood of patient response to therapy targeting the tyrosine kinase domain of *EGFR*. Contrarily, patients with wild-type *EGFR* tend to exhibit worse progression free survival if medicated with *EGFR*-TKIs than a standard chemotherapeutic regimen (Mok et al., 2009). Mutations of the *EGFR* gene vary from point mutations to indels and typically occur in exons 18-21 of the gene. The most frequently observed mutations are associated with a greater likelihood of response to *EGFR*-TKI therapy, however some mutations such as exon 20 insertions may be associated with primary resistance in the erlotinib/gefitinib-naïve setting (Lindeman et al., 2013a; Pirker et al., 2010).

The T790M mutation is thought to confer resistance to *EGFR*-TKI therapy and may be observed in cases of acquired resistance to *EGFR*-TKI therapy (Lindeman et al., 2013a). However, it must also be noted that germline T790M mutations have been observed in a small subset of patients prior to commencement of therapy (Oxnard et al., 2012). The impact of denovo sensitising and resistance mutations to *EGFR*-TKIs is currently uncertain, though scant reports suggest that patients will derive benefit from *EGFR*-TKI therapy (REFERENCE). The link between germline T790M mutation and familial cancer risk is also uncertain and patients with such a mutation profile may be candidates for closer follow up or inclusion in clinical trials.

### ALK Translocation

Translocations involving the *ALK* gene and one of a number of fusion partners are relatively infrequent events in lung cancer and occur in approximately ~5% of cases (Kwak et al., 2010), however, for those patients whose tumours exhibit an *ALK* translocation significant improvements in progression free survival can be gained by using targeted therapy such as crizotinib (Shaw et al., 2013). The main fusion partner for *ALK* is the *EML4* gene which generates the characteristic *EML4*-*ALK* translocation, however, a number of other translocation partners

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have been identified such as KIF5B (Takeuchi et al., 2009) and TFG (Rikova et al., 2007).

**ROS1 (Research Use Only)**

Mutations of the ROS1 gene are relatively rare in lung cancer and are associated with a response to treatment with the targeted therapy crizotinib in early studies (Bergethon et al., 2012). In cases where a patient's tumour does not contain mutations of either the EGFR or ALK gene then a reflex ROS1 translocation assay might be requested.

**RAS Mutation (Research Use Only\*)**

Mutations of KRAS are the most commonly observed oncogenic driver mutation in lung adenocarcinoma (Collisson et al., 2014). While there is no targeted therapy currently available for tumours expressing mutationally active RAS proteins, the mutation status may be used to select the patients for inclusion in clinical trials. The presence of a KRAS mutation may, in some cases, be used to infer the absence of another mutation.

**BRAF Mutation (Research Use Only\*)**

Mutations of the BRAF gene occur in a small percentage (<5%) of cases of lung cancer and in contrast to many other cancers which are characterised by BRAF mutations at codon 600, the mutations may be found at other codons (Paik et al., 2011). Screening for BRAF mutations in lung cancer therefore requires a broader coverage scan of exons 11 and 15 (see appendix for full description of amino acids covered). The predictive and prognostic implications of BRAF mutations in lung cancer, particularly those outside the canonical codon 600 region, are unclear.

**PIK3CA (Research Use Only\*)**

*PIK3CA* mutations have been described in a small percentage of non-small cell lung carcinomas with suggestive evidence that such mutations may be more frequently observed in squamous cell carcinomas (Collisson et al., 2014; Kawano et al., 2006; TCGA, 2012). The therapeutic and prognostic implications of *PIK3CA* mutation are as yet unclear, however, the results of this analysis may be used to select patients for clinical trials.

**HER2/ErbB2 exon 20 mutation (Research Use Only\*)**

Mutations of exon 20 of the *HER2* gene have been observed in approximately 2% of lung adenocarcinomas (Sonobe, Manabe, Wada, & Tanaka, 2006). Although scant, the number of experimental treatment options for patients with such mutations is relatively high. Patients with mutations in exon 20 of the *HER2* gene may be candidates for inclusion in a clinical trial on the basis of their mutation status.

## Colorectal Cancer Panel

The colorectal cancer mutation detection panel is designed to screen for treatment guiding mutations in the *KRAS*, *NRAS* and *BRAF* genes. All mutations are screened in parallel using the Life Technologies® Cancer Hotspot Panel version 2 assay on the Ion Torrent PGM next generation sequencer.

**Sample requirement:** FFPE block

**Tumour cellularity requirement:** >10% tumour cell content

**Tumour type:** Primary or metastatic lesion

**Average turn around time:** 7 working days

**Maximum turn around time:** 10 working days

### *KRAS* and *NRAS* mutation

Mutations in codons 12,13,61,117 and 146 of *KRAS* and codons 12,13 and 61 of *NRAS* are known to adversely affect a patient's response to anti-EGFR targeted therapy in colorectal adenocarcinoma (De Roock et al., 2010; Douillard et al., 2013). Only scant data are available for *NRAS* codons 117 and 146 due to the rarity of the mutations and if used to guide therapy a cautious approach would be warranted.

### *BRAF* V600 mutation

Approximately 8% of colorectal cancers will exhibit a *BRAF* V600 mutation. As a general rule *BRAF* V600 mutations tend to be mutually exclusive with mutations of *KRAS* or *NRAS*. *BRAF* mutations tend to be more closely associated with right-sided sessile cancers (Neumann et al., 2012). The combination of *BRAF* mutation status and microsatellite instability status may be used to indicate patient prognosis (Lochhead et al., 2013) or to aid in the diagnosis of Lynch syndrome (Bedeir & Krasinskas, 2011).

The role of *BRAF* as a predictive marker for anti-EGFR therapy is not clearly established and many studies including recent clinical trials have failed to identify a role for *BRAF* mutation in guiding anti-EGFR therapy (Douillard et al., 2013).

### *PIK3CA* mutation (Research use only)

Mutations in *PIK3CA* are not clinically validated for this panel so are not part of the standard report. If selection is required for clinical trials, please contact us to have this mutation added to the standard panel as a research use only test.

## GIST mutation Panel

The small number of cases in studies to date means that interpretation of exact mutations is quite difficult and mutations tend to be described on an exon by exon basis rather than ascribing precise effects to each mutation.

**Sample requirement:** FFPE block

**Tumour cellularity requirement:** >30% tumour cell content

**Tumour type:** Primary or metastatic lesion

**Average turn around time:** 7 working days

**Maximum turn around time:** 15 working days

### *KIT* gene mutation

Mutations of the *KIT* gene at exons 9,11,13 and 17 are associated with varying degrees of response to a family of tyrosine kinase inhibitors targeting KIT proteins and optimal dose and therapy selection can be exon dependent. Mutations in exon 14 of *KIT* may confer resistance to imatinib and are generally found in the setting of acquired resistance, however, there is some evidence to suggest that lesions with exon 14 mutations may be sensitive to sunitinib (Heinrich et al., 2008).

### *PDGFRA* gene mutation

While less frequent than mutations in *KIT*, mutations in *PDGFRA* are relatively common in GIST, being found in approximately 5% of cases, with mutations tending to be located in exons 12, 14 and 18 of the *PDGFRA* gene (Corless et al., 2005). Mutations in exons 12, 14 and 18 are thought to confer increased sensitivity to therapy targeting mutationally active PDGFRA. Specific exceptions to this rule can be found in the literature, for example, D842 mutations are thought to confer a more resistant phenotype to imatinib and sunitinib (Heinrich et al., 2003, 2008).

### *BRAF* V600 mutation

Mutations in codon 600 of the BRAF gene are a feature of many cancers including GIST however the frequency of mutations is quite low (<1%). While data on the impact of BRAF mutations in GIST is scant, some reports seem to suggest that it may negatively impact the response to imatinib in patients who harbour a concurrent sensitising mutation (Miranda et al., 2012). Secondary BRAF mutations have been suggested as a causal mutation in acquired resistance to imatinib in GIST (Agaram et al., 2008).

GIST responsiveness to agents targeting mutated BRAF protein is currently unknown but patients with a *BRAF* V600 mutation may be eligible for inclusion in a clinical trial on the basis of the result.



## Melanoma mutation panel

Melanoma is a highly aggressive form of skin cancer and accounts for a disproportionate number of cancer deaths relative to non-melanoma skin cancer. The mutational landscape of melanoma is dominated by mutations of the BRAF gene (Hodis et al., 2012). In addition NRAS mutation is frequently observed and mutations of the KIT gene are observed in a number of cases where it may be used to guide therapy.

**Sample requirement:** FFPE block

**Tumour cellularity requirement:** >10% tumour cell content (ideally >30%)

**Tumour type:** Primary or preferably metastatic lesion \*\*

**Average turn around time:** 5 working days

**Maximum turn around time:** 10 working days

### BRAF V600

Mutations of the BRAF gene are a common feature of melanoma. The majority of mutations of this gene are found in codon 600 and involve a change at amino acid level from a valine to the glutamic acid (V600E). While the mutation rate of BRAF in cutaneous melanoma is thought to be approximately 50%, evidence is starting to accumulate that a lower mutation frequency in the BRAF gene is a feature of melanoma in the Irish setting (van den Hurk et al., 2015).

In melanoma patients, response to targeted therapies such as vemurafinib is strongly associated with the presence of a somatic mutation at codon 600 of the BRAF gene, therefore the determination of BRAF mutation status prior to commencement of therapy is a prescription requirement (da Rocha Dias et al., 2013).

Mutations outside of the V600 codon of BRAF are infrequent relative to the dominant V600 mutations and are not used to stratify patients for standard of care therapy.

### NRAS

NRAS mutations occur with a frequency of approximately 15% to 26% in melanoma and tend to be mutually exclusive with mutations of the BRAF gene (Colombino et al., 2012; Hodis et al., 2012). While NRAS mutations are relatively frequent and a likely driver in a subset of melanoma cases, no targeted therapy currently exists for NRAS. However, driver mutations in NRAS may be independent prognostic factors in melanoma (Jakob et al., 2012) or may be used to select patients for inclusion in clinical trials.

It has also been suggested that NRAS mutation may play a role in therapeutic resistance to imatinib (Hodi et al., 2013) and vemurafinib (Nazarian et al., 2010). Whether the mutations are implicated in acquired or primary resistance to therapy is unclear.

***KIT***

Mutation and copy number variation of the KIT gene are relatively common occurrences in melanoma at 3% and 6% respectively (Hodis et al., 2012). The melanoma panel has the capacity to detect mutations, but not copy number variations, in a number of coding exons in KIT. Mutations of the KIT gene have been associated with response to treatment with specific tyrosine kinase inhibitors such as imatinib (Carvajal et al., 2011; Hodi et al., 2013).

**\*\*In cases of melanoma relapse a biopsy of the recurrent metastatic lesion would be preferable**

## 50 Gene Cancer Hotspot panel (Research Use Only)

The 50 gene Cancer Hotspot Panel version 2 assay from Life Technologies is used as the basis for the full research panel. Analysis follows the same clinically validated workflow as for our standard of care assays, however for those assays outside of the scope of our accreditation the same degree of validation cannot be ensured so such assays are designated for research use only. In addition to the differences at a validation level, samples are reviewed manually in addition to the standard bioinformatic pipeline to ensure that known areas of poor coverage are selected for manual correction where necessary.

5 of the genes in the panel are validated for clinical use (KRAS, NRAS, BRAF, KIT and PDGFRA), the remaining 45 genes are offered as a full screen, as part of tumour specific panels or individual genes can be selected for specific analysis. Retrospective bioinformatic analysis of samples tested using the same platform is possible for patient selection for clinical trials (with patient consent).

To have samples tested using the 50 gene panel for clinical trials selection please email Prof Stephen Finn ([stephen.finn@tcd.ie](mailto:stephen.finn@tcd.ie)). For analysis as a research service please email Dr Cathal O'Brien ([cpobrien@stjames.ie](mailto:cpobrien@stjames.ie)).

## Assay specification

### Roche Cobas EGFR assay

The EGFR test detects any of 41 mutations in the EGFR gene with 2 targets being mutation specific. The other 39 are detected if present but are grouped into 4 types; G719 mutations in exon 18, deletions from exon 19, insertions in exon 20 and L858R mutations in exon 21. The table below shows the full detailed list of the base changes and their detection using the Roche Cobas® EGFR mutation assay.

<i><b>Mutation</b></i>	<i><b>AA Change</b></i>	<i><b>COSMIC ID</b></i>
<b>Exon 18 – Mutation call G719X</b>		
2155 G>A	G719S	6252
2155 G>T	G719C	6253
2156 G>C	G719A	6239
<b>Exon 19 – Mutation call exon 19 Deletion</b>		
2235 2249del15	E746 A750del	6223
2236 2250del15	E746 A750del	6225
2240 2257del18	L747 P753>S	12370
2240 2254del15	L747 T751del	12369
2239 2256del18	L747 S752del	6255
2239 2251>C	L747 T751>P	12383
2237 2251del15	E746 T751>A	12678
2237 2255>T	E746 S752>V	12384
2239 2248TTAAGAGAAG>C	E747 A750>P	12382
2239 2253del15	L747 T751del	6254
2239 2247del9	L747 E749del	6218
2235 2252>AAT	E746 T751>I	13551
2236 2253del18	E746 T751del	12728
2237 2254del18	E746 S752>A	12367
2238 2255del18	E746 S752>D	6220
2238 2248>GC	L747 A750>P	12422
2238 2252>GCA	L747 T751>Q	12419
2239 2258>CA	L747 P753>Q	12387
2240 2251del12	L747 T751>S	6210
2233 2247del15	K745 E749del	26038
2253 2276del24	S752 I759del	13556
2235 2248>AATTC	E746 A750>IP	13550
2237 2252>T	E746 T751>V	12386
2235 2251>AATTC	E746 T751>IP	13552
2235 2255>AAT	E746 S752>I	12385
2237 2253>TTGCT	E746 T751>VA	12416
2237 2257>TCT	E746 P753>VS	18427
2238 2252del15	L747 T751del	23571
2239 2256>CAA	L747 S752>Q	12403

<b>Mutation</b>	<b>AA Change</b>	<b>COSMIC ID</b>
<b>Exon 20 – Mutation calls T790M, S768I, exon 20 insertion</b>		
2303 G>T	S768I	6241
2369 C>T	T790M	6240
2319_2320insCAC	H773_V774insH	12377
2310_2311insGGT	D770_N771insG	12378
2307_2308ins9GCCAGCGTG	V769_D770insASV	12376
2309_2310AC>CCAGCGTGGAT	V769_D770insASV	13558
2311_2312ins9GCGTGGACA	D770_N771insSVD	13428
<b>Exon 21 –Mutation call L858R</b>		
2573 T>G	L858R	6224
2573_2574TG>GT	L858R	12429

Details of each mutation detected and details of the base change are listed. Cosmic ID's are taken from the Catalogue of Somatic Mutations in Cancer<sup>1</sup>.

1. <http://www.sanger.ac.uk/genetics/CGP/cosmic/>

### ALK rearrangement assay

The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens. The Vysis kit operates as a gene specific breakapart probe and permits the detection of any chromosomal break in the ALK gene. As the breakapart assay detects any rearrangement of the ALK gene it is capable of detecting the most common EML4-ALK rearrangement in addition to rearrangements involving other partner genes.

As FISH testing was used in the major clinical trials establishing the efficacy of crizotinib therapy in lung adenocarcinoma (Shaw et al., 2013) it is regarded as the standard of care test for the detection of treatment guiding ALK rearrangements in non small cell lung adenocarcinoma (Lindeman et al., 2013b).

### ALK immunohistochemistry

In cases where the standard of care FISH assay is technically unfeasible, an immunohistochemistry assay is employed as a backup. As the assay is not the standard of care assay and is often employed on substandard tissue the results must be interpreted with a greater degree of caution than one might apply to results generated using the FISH assay.

### ROS1 rearrangement assay

The ROS1 rearrangement kit uses a pair of fluorescent probes located proximal to the 5' and 3' genomic regions of the *ROS1* gene. Both probes can be identified as being adjacent microscopically in normal chromosomes. Where present, translocations involving the *ROS1* gene result in relocation of the probes generating a characteristic split signal. As a breakapart assay, the *ROS1* rearrangement assay is capable of detecting rearrangements involving a number of fusion partners.

**Next generation sequencing (NGS) panels**

The colorectal, GIST and Melanoma panels use a common chemistry and bioinformatic pipeline to simultaneously assess mutation status in known cancer mutation hotspots of 50 genes. Of the 50 genes on the panel 5 are validated for direct use in clinical decision-making. The remaining 45 gene hotspots are not analysed using the bioinformatic pipeline but can be retrospectively analysed if required for clinical trials or research use if the appropriate ethical approval has been obtained.

Exon coverage for each assay may not be complete as the assay is designed to detect hotspot mutations. As a result one should be guided by the list of clinically validated mutations (Appendix 1) and the amino acid coverage for each exon (Appendix 2).

## Appendix 1: Clinically validated mutations for Colorectal, GIST and Melanoma panels

Mutations below encompass those mutations that are specifically assessed by the panel. Other, less common mutations may also be detected by the panel but are dependent on panel design. For treatment guiding assays, known SNPs and silent mutations are not reported.

Gene	Exon	Nucleotide Change	Amino acid change
NRAS	4	c.436G>A	p.A146X
NRAS	4	c.436G>T	p.A146X
NRAS	4	c.436G>C	p.A146X
NRAS	3	c.193A>T	p.S65C
NRAS	3	c.183A>T	p.Q61H
NRAS	3	c.183A>T	p.Q61H
NRAS	3	c.183A>G	p.Q61Q
NRAS	3	c.182>183AA>TG	p.Q61L
NRAS	3	c.182>183AA>GG	p.Q61R
NRAS	3	c.181>183CAA>AAG	p.Q61K
NRAS	3	c.182A>G	p.Q61P
NRAS	3	c.182A>T	p.Q61L
NRAS	3	c.182A>G	p.Q61R
NRAS	3	c.181>182CA>TT	p.Q61L
NRAS	3	c.181>182CA>AG	p.Q61R
NRAS	3	c.181C>A	p.Q61K
NRAS	3	c.181C>G	p.Q61E
NRAS	3	c.180>181AC>TA	p.Q61K
NRAS	3	c.179G>A	p.G60E
NRAS	2	c.52G>A	p.A18T
NRAS	2	c.39T>C	p.G13G
NRAS	2	c.39>39GT>TC	p.G13V
NRAS	2	c.38G>A	p.G13D
NRAS	2	c.38G>T	p.G13V
NRAS	2	c.38G>C	p.G13A
NRAS	2	c.37G>C	p.G13R
NRAS	2	c.37G>T	p.G13C
NRAS	2	c.38G>A	p.G13S
NRAS	2	c.36T>C	p.G12G
NRAS	2	c.35G>A	p.G12D



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NRAS	2	c.35G>C	p.G12A
NRAS	2	c.35G>T	p.G12v
NRAS	2	c.34>35GG>AA	p.G12N
NRAS	2	c.34G>C	p.G12R
NRAS	2	c.34G>T	p.G12C
NRAS	2	c.34G>A	p.G12S
NRAS	2	c.31G>A	p.A11T
PDGFRA	12	c.1659_1664delGAGGTA	p.R554_Y555delRY
PDGFRA	12	c.1678_1692del15	p.R560_S564delRVIES
PDGFRA	12	c.1682T>A	p.V561D
PDGFRA	12	c.1694_1695insA	p.S566fs*6
PDGFRA	12	c.1697_1711del15	p.p.S566_E571>K
PDGFRA	12	c.1698_1712del15	p.S566_E571>R
PDGFRA	14	c.1975A>T	p.N659Y
PDGFRA	14	c.1977C>G	p.N659K
PDGFRA	14	c.1977C>A	p.N659K
PDGFRA	18	c.2472C>T	p.V824V
PDGFRA	18	c.2521_2526delAGAGAC	p.R841_D842delRD
PDGFRA	18	c.2524G>T	p.D842Y
PDGFRA	18	c.2524_2525GA>AT	p.D842I
PDGFRA	18	c.2524_2526GAC>TAT	p.D842Y
PDGFRA	18	c.2524_2526delGAC	p.D842delD
PDGFRA	18	c.2524_2532delGACATCATG	p.D842_M844delDIM
PDGFRA	18	c.2524_2535del12	p.I843_D846delIMHD
PDGFRA	18	c.2524_2536>A	p.D842_D846>N
PDGFRA	18	c.2525A>T	p.D842V
PDGFRA	18	c.2526_2537del12	p.I843_D846delIMHD
PDGFRA	18	c.2526_2538>G	p.D842_D846>E
PDGFRA	18	c.2527_2538del12	p.I843_D846delIMHD
PDGFRA	18	c.2528_2539del12	p.I843_S847>T
PDGFRA	18	c.2530_2541del12	p.M844_S847delMHDS
PDGFRA	18	c.2536G>T	p.D846Y
KIT	9	c.1509_1510insGCCTAT	p.Y503_F504insAY
KIT	9	c.1526A>T	p.K509I
KIT	11	c.1651_1665del15	p.P551_V555del
KIT	11	c.1652C>T	p.P551L
KIT	11	c.1653_1670del18	p.M552_W557del
KIT	11	c.1654A>C	p.M552L
KIT	11	c.1654_1659delATGTAT	p.M552_Y553del

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KIT	11	c.1654_1662del9	p.M552_E554del
KIT	11	c.1654_1668del15	p.M552_Q556del
KIT	11	c.1654_1671del18	p.M552_W557del
KIT	11	c.1655_1660delTGATG	p.M552_E554>K
KIT	11	c.1655_1666del12	p.M552_Q556>K
KIT	11	c.1655_1672del18	p.M552_W557del
KIT	11	c.1656_1670del15	p.Y553_W557del
KIT	11	c.1656_1673del18	p.Y553_K558
KIT	11	c.1657T>A	p.Y553N
KIT	11	c.1657_1668del12	p.Y553_Q556del
KIT	11	c.1657_1674del18	p.Y553_K558del
KIT	11	c.1658_1720del63	p.Y553_T574>S
KIT	11	c.1660G>A	p.E554K
KIT	11	c.1660_1674del15	p.E554_K558del
KIT	11	c.1661_1675del15	p.E554_K558del
KIT	11	c.1662_1685del24	p.V555_E562del
KIT	11	c.1663G>A	p.V555I
KIT	11	c.1663_1668delGTACAG	p.V555_Q556del
KIT	11	c.1663_1674del12	p.V555_K558del
KIT	11	c.1663_1677del15	p.V555_V559del
KIT	11	c.1663_1680del18	p.V555_V560del
KIT	11	c.1663_1713del51	p.V555_I571del
KIT	11	c.1663_1719del57	p.V555_P573del
KIT	11	c.1666_1680del15	p.Q556_K558del
KIT	11	c.1666_1728del63	p.Q556_L576del
KIT	11	c.1667_1672delAGTGGA	p.W557_K558del
KIT	11	c.1667_1681del15	p.W557_E561del
KIT	11	c.1668_1673delGTGGAA	p.W557_K558del
KIT	11	c.1668_1679del12	p.Q556_V560>H
KIT	11	c.1669T>A	p.W557R
KIT	11	c.1669T>C	p.W557R
KIT	11	c.1669T>G	p.W557G
KIT	11	c.1669_1671delTGG	p.W557del
KIT	11	c.1669_1672TGGGA>G	p.W557_K558>E
KIT	11	c.1669_1674delTGGGAAG	p.W557_K558del
KIT	11	c.1669_1674delTGGGAAG	p.W557_K558del
KIT	11	c.1669_1677del9	p.W557_V559del
KIT	11	c.1669_1680del12	p.W557_V560del

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KIT	11	c.1669_1683del15	p.W557_E561del
KIT	11	c.1670G>C	p.W557S
KIT	11	c.1670_1675delGGAAGG	p.W557_V559>F
KIT	11	c.1670_1717del48	p.W557
KIT	11	c.1671_1673GAA>TCC	p.W557_K558>CP
KIT	11	c.1671_1676delGAAGGT	p.W557_V559>C
KIT	11	c.1671_1679del9	p.W557_V560>C
KIT	11	c.1672A>G	p.K558E
KIT	11	c.1672_1676AAGGT>TCTTC	p.K558_V559>SS
KIT	11	c.1672_1677delAAGGTT	p.K558_V559del
KIT	11	c.1672_1680del9	p.K558_V560del
KIT	11	c.1672_1686del15	p.K558_E562del
KIT	11	c.1672_1692del21	p.K558_N564del
KIT	11	c.1673A>G	p.K558R
KIT	11	c.1673_1678delAGGTTG	p.K558>V560>I
KIT	11	c.1673_1687del15	p.K558>E562del
KIT	11	c.1673_1674insTCC	p.K558>NP
KIT	11	c.1674G>A	p.K558K
KIT	11	c.1674_1674G>TCCT	p.K558>NP
KIT	11	c.1674_1679delGGTTGT	p.K558>V560>N
KIT	11	c.1675G>A	p.V559I
KIT	11	c.1675_1677delGTT	p.V559del
KIT	11	c.1675_1680delGTTGTT	p.V559_V560del
KIT	11	c.1675_1683del9	p.V559_E561del
KIT	11	c.1675_1695del21	p.V559_G565del
KIT	11	c.1676T>A	p.V559D
KIT	11	c.1676T>G	p.V559G
KIT	11	c.1676T>C	p.V559A
KIT	11	c.1676_1684del9	p.V559_E561del
KIT	11	c.1678_1680delGTT	p.V560del
KIT	11	c.1678_1728del51	p.V560_L576del
KIT	11	c.1679T>A	p.V560D
KIT	11	c.1679T>G	p.V560G
KIT	11	c.1679_1680TT>AG	p.V560E
KIT	11	c.1679_1681delTTG	p.V560del
KIT	11	c.1681G>A	p.E561K
KIT	11	c.1683G>A	p.E561E
KIT	11	c.1684G>A	p.E562K
KIT	11	c.1687_1728del42	p.I563_L576del

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KIT	11	c.1690_1728del39	p.N564_L576del
KIT	11	c.1690_1734del45	p.N564_Y578del
KIT	11	c.1696A>G	p.N566D
KIT	11	c.1698C>T	p.N566N
KIT	11	c.1701T>A	p.N567K
KIT	11	c.1702T>G	p.Y568D
KIT	11	c.1702_1722del21	p.Y568_T574del
KIT	11	c.1708_1728del21	p.Y570_L576del
KIT	11	c.1711_1728del18	p.I571_L576del
KIT	11	c.1714G>A	p.D572N
KIT	11	c.1718C>T	p.P573L
KIT	11	c.1726C>T	p.L576F
KIT	11	c.1726>1728delCTT	p.L576del
KIT	11	c.1727T>C	p.L576P
KIT	11	c.1729C>T	p.P577S
KIT	11	c.1735_1737delGAT	p.D579del
KIT	11	c.1745G>A	p.W582*
KIT	11	c.1746G>A	p.W582*
KIT	11	c.1751T>C	p.F584S
KIT	11	c.1755C>T	p.P585P
KIT	13	c.1924A>G	p.K642E
KIT	13	c.1928T>C	p.V643A
KIT	13	c.1961T>C	p.V654A
KIT	14	c.2008>2009AC>GA	p.T670E
KIT	14	c.2009C>T	p.T670I
KIT	17	c.2433T>C	p.F811F
KIT	17	c.2446G>T	p.D816Y
KIT	17	c.2446G>C	p.D816H
KIT	17	c.2446_2447GA>TT	p.D816F
KIT	17	c.2446_2447GA>AT	p.D816I
KIT	17	c.2447A>G	p.D816G
KIT	17	c.2447A>T	p.D816V
KIT	17	c.2448C>G	p.D816E
KIT	17	c.2453A>G	p.K818R
KIT	17	c.2458G>T	p.D820Y
KIT	17	c.2458G>C	p.D820H
KIT	17	c.2459A>G	p.D820G
KIT	17	c.2459A>T	p.D820V
KIT	17	c.2460T>A	p.D820E

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KIT	17	c.2464A>T	p.N822Y
KIT	17	c.2466T>A	p.N822K
KIT	17	c.2466T>G	p.N822K
KIT	17	c.2467T>G	p.Y823D
KIT	17	c.2468A>G	p.Y823C
KIT	17	c.2473G>A	p.V825I
KIT	17	c.2474T>C	p.V825A
BRAF	15	c.1799_1801delTGA	p.V600_K601>E
BRAF	15	c.1799_1800TG>AA	p.V600E
BRAF	15	c.1799_1800TG>AT	p.V600D
BRAF	15	c.1799T>C	p.V600A
BRAF	15	c.1799T>A	p.V600E
BRAF	15	c.1799T>G	p.V600G
BRAF	15	c.1798_1977GT>CA	p.V600Q
BRAF	15	c.1798_1799GT>AA	p.V600K
BRAF	15	c.1798_1799GT>AG	p.V600R
BRAF	15	c.1797_1799AGT>GAG	p.V600R
BRAF	15	c.1798G>A	p.V600M
BRAF	15	c.1798G>C	p.V600L
BRAF	15	c.1798G>T	p.V600L
KRAS	4	c.437C>T	p.A146V
KRAS	4	c.436G>A	p.A146T
KRAS	4	c.436G>C	p.A146P
KRAS	4	c.351A>C	p.K117N
KRAS	4	c.351A>T	p.K117N
KRAS	3	c.183A>C	p.Q61H
KRAS	3	c.183A>T	p.Q61H
KRAS	3	c.182A>C	p.Q61P
KRAS	3	c.182A>G	p.Q61R
KRAS	3	c.182A>T	p.Q61L
KRAS	3	c.181C>A	p.Q61K
KRAS	3	c.181C>G	p.Q61E
KRAS	3	c.180_181TC>AA	p.Q61K
KRAS	3	c.176C>G	p.A59G
KRAS	3	c.176C>A	p.A59E
KRAS	3	c.175G>A	p.A59T
KRAS	2	c.39C>G	p.G13G
KRAS	2	c.39C>T	p.G13G
KRAS	2	c.39C>A	p.G13G

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KRAS	2	c.38_39GG>TT	p.G13V
KRAS	2	c.38_39GC>TG	p.G13V
KRAS	2	c.38_39GC>AT	p.G13D
KRAS	2	c.38_39GC>AA	p.G13E
KRAS	2	c.37_39GGC>CGT	p.G13R
KRAS	2	c.38G>A	p.G13D
KRAS	2	c.38G>C	p.G13A
KRAS	2	c.38G>T	p.G13V
KRAS	2	c.37G>T	p.G13C
KRAS	2	c.37G>A	p.G13S
KRAS	2	c.37G>C	p.G13R
KRAS	2	c.36_37TG>AT	p.G13C
KRAS	2	c.36_37insGGT	p.G12>G13insG
KRAS	2	c.36T>C	p.G12G
KRAS	2	c.36T>A	p.G12G
KRAS	2	c.35_36GT>AC	p.G12D
KRAS	2	c.36_36GT>TC	p.G12V
KRAS	2	c.35_36GT>AA	p.G12E
KRAS	2	c.34_36GGT>TGG	p.G12W
KRAS	2	c.34_36GGT>TGC	p.G12C
KRAS	2	c.35G>T	p.G12V
KRAS	2	c.35G>A	p.G12D
KRAS	2	c.35G>C	p.G12A
KRAS	2	c.34_35GG>TA	p.G12Y
KRAS	2	c.34_35GG>AT	p.G12I
KRAS	2	c.34_35GG>TT	p.G12F
KRAS	2	c.34_35GG>CT	p.G12L
KRAS	2	c.34G>T	p.G12C
KRAS	2	c.34G>A	p.G12S
KRAS	2	c.34G>C	p.G12R

## Appendix 2: Genes with mutation hotspots detected by the Cancer Hotspot Panel

<i>Gene</i>	<i>Exon</i>	<i>Amino acid range</i>	<i>Reference</i>	<i>Chromosome</i>
ABL1	4	248-279	NM_007313	9
ABL1	5	294-299	NM_007313	9
ABL1	6	334-378	NM_007313	9
ABL1	7	400-431	NM_007313	9
AKT	3	17-51	NM_005163	14
AKT	6	155-182	NM_005163	14
ALK	13	1173-1203	NM_004303	2
ALK	25	1270-1278	NM_004303	2
APC	16	861-890	NM_000038	5
APC	16	1090-1125	NM_000038	5
APC	16	1285-1325	NM_000038	5
APC	16	1343-4384	NM_000038	5
APC	16	1427-1470	NM_000038	5
APC	16	1484-1523	NM_000038	5
APC	16	1544-1581	NM_000038	5
ATM	8	327-355	NM_000051	11
ATM	9	408-411	NM_000051	11
ATM	12	602-625	NM_000051	11
ATM	17	835-864	NM_000051	11
ATM	26	1293-1324	NM_000051	11
ATM	34	1625-1707	NM_000051	11
ATM	35	1727-1756	NM_000051	11
ATM	36	1791-1814	NM_000051	11
ATM	39	1927-1945	NM_000051	11
ATM	50	2437-2453	NM_000051	11
ATM	54	2651-2666	NM_000051	11
ATM	55	2683-2710	NM_000051	11
ATM	56	2718-2763	NM_000051	11
ATM	59	2866-2890	NM_000051	11
ATM	61	2934-2950	NM_000051	11
ATM	63	2997-3025	NM_000051	11
ATM	63	3042-3057	NM_000051	11
BRAF	11	440-472	NM_004333	7
BRAF	15	582-610	NM_004333	7
CDH1	3	66-96	NM_004360	16

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CDH1	8	337-374	NM_004360	16
CDH1	9	380-408	NM_004360	16
CDKN2A	2	98-139	NM_000077	9
CDKN2A	2	51-89	NM_000077	9
CSF1R	7	293-318	NM_005211	5
CSF1R	22	954-973	NM_005211	5
CTNNB1	3	10-48	NM_001904	3
EGFR	3	97-123	NM_005228	7
EGFR	7	280-296	NM_005228	7
EGFR	15	575-601	NM_005228	7
EGFR	18	969-725	NM_005228	7
EGFR	19	729-761	NM_005228	7
EGFR	20	762-796	NM_005228	7
EGFR	20	808-823	NM_005228	7
EGFR	21	856-875	NM_005228	7
ERBB2	19	753-769	NM_000448	17
ERBB2	20	770-796	NM_000448	17
ERBB2	21	840-881	NM_000448	17
ERBB4	3	137-140	NM_005235	2
ERBB4	4	168-185	NM_005235	2
ERBB4	6	226-246	NM_005235	2
ERBB4	7	255-289	NM_005235	2
ERBB4	8	296-322	NM_005235	2
ERBB4	9	334-366	NM_005235	2
ERBB4	15	581-622	NM_005235	2
ERBB4	23	920-947	NM_005235	2
EZH2		620-644	NM_001203247	7
FBXW7	5	265-287	NM_033632	4
FBXW7	8	379-402	NM_033632	4
FBXW7	9	435-472	NM_033632	4
FBXW7	10	479-508	NM_033632	4
FBXW7	11	567-593	NM_033632	4
FGFR1	4	121-149	NM_001774063	8
FGFR1	7	250-274	NM_001774063	8
FGFR2	7	297-313	NM_001144917	10
FGFR2	7	250-274	NM_001144917	10
FGFR2	9	363-398	NM_001144917	10
FGFR2	12	546-557	NM_001144917	10
FGFR3	7	248-277	NM_000142	4



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FGFR3	9	368-402	NM_000142	4
FGFR3	14	632-653	NM_000142	4
FGFR3	16	691-719	NM_000142	4
FGFR3	18	772-807	NM_000142	4
FLT3	11	438-465	NM_004119	13
FLT3	14	570-609	NM_004119	13
FLT3	16	664-684	NM_004119	13
FLT3	20	828-247	NM_004119	13
GNA11	5	203-219	NM_002067	19
GNAQ	5	245-206	NM_002072	9
GNAS	8	196-219	NM_000516	20
GNAS	9	221-239	NM_000516	20
HNF1A	3	193-221	NM_000545	12
HNF1A	4	254-282	NM_000545	12
HRAS	2	6-34	NM_005343	11
HRAS	3	43-81	NM_005343	11
IDH2	4	134-176	NM_002168	15
JAK2	14	604-621	NM_004972	9
JAK3	4	129-140	NM_000215	19
JAK3	13	568-579	NM_000215	19
JAK3	16	710-733	NM_000215	19
KDR	6	245-266	NM_002253	4
KDR	7	267-290	NM_002253	4
KDR	11	472-479	NM_002253	4
KDR	19	873-893	NM_002253	4
KDR	21	961-987	NM_002253	4
KDR	26	1136-1155	NM_002253	4
KDR	27	1193-1220	NM_002253	4
KDR	30	1325-13557	NM_002253	4
KDR	30	1284-1309	NM_002253	4
KIT	2	24-59	NM_000222	4
KIT	9	495-509	NM_000222	4
KIT	10	526-549	NM_000222	4
KIT	11	551-589	NM_000222	4
KIT	13	628-660	NM_000222	4
KIT	14	665-682	NM_000222	4
KIT	15	715-724	NM_000222	4
KIT	17	798-828	NM_000222	4
KIT	18	832-860	NM_000222	4

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KRAS	2	6-37	NM_033360	12
KRAS	3	38-65	NM_033360	12
KRAS	4	114-149	NM_033360	12
MET	2	160-187	NM_000245	7
MET	2	340-377	NM_000245	7
MET	11	799-837	NM_000245	7
MET	14	964-994	NM_000245	7
MET	16	1088-1113	NM_000245	7
MET	19	1229-1255	NM_000245	7
MLH1	12	374-414	NM_000249	3
MPL	10	502-521	NM_005373	1
NOTCH1	26	1566-1602	NM_017617	9
NOTCH1	27	1674-1679	NM_017617	9
NOTCH1	34	2436-2476	NM_017617	9
NPM1	11	283-295	NM_002520	5
NRAS	2	5-31	NM_002524	1
NRAS	3	40-70	NM_002524	1
NRAS	4	121-150	NM_002524	1
PDGFRA	12	552-583	NM_006206	4
PDGFRA	14	644-667	NM_006206	4
PDGFRA	15	672-710	NM_006206	4
PDGFRA	18	816-853	NM_006206	4
PIK3CA	2	55-89	NM_006218	3
PIK3CA	2	107-117	NM_006218	3
PIK3CA	5	317-350	NM_006218	3
PIK3CA	7	391-417	NM_006218	3
PIK3CA	8	418-421	NM_006218	3
PIK3CA	8	450-468	NM_006218	3
PIK3CA	10	523-549	NM_006218	3
PIK3CA	14	678-720	NM_006218	3
PIK3CA	19	899-923	NM_006218	3
PIK3CA	21	1018-1050	NM_006218	3
PIK3CA	21	1066-1069	NM_006218	3
PTEN	1	1-25	NM_000314	10
PTEN	3	56-69	NM_000314	10
PTEN	5	100-134	NM_000314	10
PTEN	6	165-183	NM_000314	10
PTEN	7	212-215	NM_000314	10
PTEN	7	232-266	NM_000314	10

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PTEN	8	283-299	NM_000314	10
PTEN	8	313-341	NM_000314	10
PTPN11	3	47-81	NM_002834	12
PTPN11	13	487-527	NM_002834	12
RB1	4	131-159	NM_000321	13
RB1	6	197-202	NM_000321	13
RB1	10	314-344	NM_000321	13
RB1	11	351-366	NM_000321	13
RB1	14	453-463	NM_000321	13
RB1	17	578-565	NM_000321	13
RB1	18	566-581	NM_000321	13
RB1	20	656-690	NM_000321	13
RB1	21	703-724	NM_000321	13
RB1	22	744-769	NM_000321	13
RET	10	608-626	NM_020975	10
RET	11	628-653	NM_020975	10
RET	13	763-785	NM_020975	10
RET	15	877-909	NM_020975	10
RET	16	911-923	NM_020975	10
SMAD4	3	99-135	NM_005359	18
SMAD4	4	143-145	NM_005359	18
SMAD4	5	166-202	NM_005359	18
SMAD4	6	234-262	NM_005359	18
SMAD4	8	308-318	NM_005359	18
SMAD4	9	327-364	NM_005359	18
SMAD4	10	385-423	NM_005359	18
SMAD4	11	444-473	NM_005359	18
SMAD4	12	495-532	NM_005359	18
SMARCB1	2	36-72	NM_003073	22
SMARCB1	4	145-166	NM_003073	22
SMARCB1	5	168-205	NM_003073	22
SMARCB1	9	374-386	NM_003073	22
SMO	3	187-227	NM_005631	7
SMO	5	308-331	NM_005631	7
SMO	6	392-418	NM_005631	7
SMO	9	512-542	NM_005631	7
SMO	11	609-645	NM_005631	7
SRC	14	500-532	NM_005417	20
STK11	1	23-64	NM_000455	19

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STK11	4	156-181	NM_000455	19
STK11	4	192-199	NM_000455	19
STK11	5	200-207	NM_000455	19
STK11	6	254-285	NM_000455	19
STK11	8	318-360	NM_000455	19
TP53	2	1-20	NM_000546	17
TP53	4	68-112	NM_000546	17
TP53	5	150-186	NM_000546	17
TP53	5	126-137	NM_000546	17
TP53	6	188-222	NM_000546	17
TP53	7	225-257	NM_000546	17
TP53	8	263-306	NM_000546	17
TP53	10	332-367	NM_000546	17
VHL	1	79-107	NM_000551	3
VHL	2	115-150	NM_000551	3
VHL	3	156-173	NM_000551	3

### Appendix 3: Oncomine Focus Hotspot coverage

#### Mutation hotspots

Gene	Exon	Amino Acids	Accession	Chromosome
AKT1	3	17-51	NM_005163	14
ALK	11	660-680	NM_004304	2
ALK	21	1121-1150	NM_004304	2
ALK	22	1151-1171	NM_004304	2
ALK	23	1173-1214	NM_004304	2
ALK	24	1217-1247	NM_004304	2
ALK	25	1252-1277	NM_004304	2
ALK	27	1334-1357	NM_004304	2
ALK	29	1584-1620	NM_004304	2
ALK	29	1499-1541	NM_004304	2
ALK	29	1428-1470	NM_004304	2
BRAF	5	204-228	NM_004333	7
BRAF	6	249-273	NM_004333	7
BRAF	7	288-309	NM_004333	7
BRAF	8	328-349	NM_004333	7
BRAF	10	418-438	NM_004333	7
BRAF	11	451-477	NM_004333	7
BRAF	13	594-565	NM_004333	7
BRAF	13	507-513	NM_004333	7
BRAF	15	582-610	NM_004333	7
BRAF	18	736-766	NM_004333	7
CDK4	2	8-49	NM_000075	12
CDK4	5	190-210	NM_000075	12
CDK4	6	212-224	NM_000075	12
CDK4	7	268-273	NM_000075	12
CDK4	8	286-302	NM_000075	12
CTNNB1	3	10-47	NM_001904	3
DDR2	5	93-134	NM_006182	1
EGFR	3	97-123	NM_005228	7
EGFR	7	280-296	NM_005228	7
EGFR	12	474-499	NM_005228	7
EGFR	15	575-601	NM_005228	7
EGFR	18	695-725	NM_005228	7
EGFR	19	729-761	NM_005228	7
EGFR	20	762-799	NM_005228	7
EGFR	21	827-865	NM_005228	7

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ERBB2	8	302-326	NM_004448	17
ERBB2	17	662-690	NM_004448	17
ERBB2	18	704-736	NM_004448	17
ERBB2	19	753-769	NM_004448	17
ERBB2	20	770-796	NM_004448	17
ERBB2	21	840-881	NM_004448	17
ERBB2	22	884-904	NM_004448	17
ERBB2	24	969-989	NM_004448	17
ERBB2	25	1010-1050	NM_004448	17
ERBB3	2	47-77	NM_001982	12
ERBB3	3	88-120	NM_001982	12
ERBB3	6	206-244	NM_001982	12
ERBB3	8	293-312	NM_001982	12
ERBB3	9	331-369	NM_001982	12
ERBB4	18	694-713	NM_005235	2
ESR1	8	533-572	NM_00125	6
FGFR2	7	251-274	NM_000141	10
FGFR2	8	315-348	NM_000141	10
FGFR2	9	363-398	NM_000141	10
FGFR2	12	546-557	NM_000141	10
FGFR2	14	631-662	NM_000141	10
FGFR3	3	80-121	NM_000142	4
FGFR3	7	248-277	NM_000142	4
FGFR3	9	368-402	NM_000142	4
FGFR3	14	632-653	NM_000142	4
FGFR3	16	691-719	NM_000142	4
GNA11	4	168-201	NM_002067	19
GNA11	5	203-219	NM_002067	19
GNAQ	4	166-195	NM_002072	9
GNAQ	5	206-245	NM_002072	9
HRAS	2	1-25	NM_005343	11
HRAS	3	43-81	NM_005343	11
IDH1	4	101-134	NM_005896	2
IDH2	4	134-176	NM_002168	15
JAK1	14	638-662	NM_002227	1
JAK1	15	686-705	NM_002227	1
JAK1	16	706-742	NM_002227	1
JAK2	14	604-621	NM_004972	9
JAK3	11	484-507	NM_000215	19
JAK3	12	525-567	NM_000215	19
JAK3	15	641-681	NM_000215	19

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KIT	8	412-433	NM_000222	4
KIT	9	495-513	NM_000222	4
KIT	10	526-549	NM_000222	4
KIT	11	550-587	NM_000222	4
KIT	13	628-660	NM_000222	4
KIT	17	792-828	NM_000222	4
KRAS	2	6-36	NM_004985	12
KRAS	3	38-65	NM_004985	12
KRAS	4	114-149	NM_004985	12
MAP2K1	2	44-81	NM_002755	15
MAP2K1	3	106-144	NM_002755	15
MAP2K1	6	191-225	NM_002755	15
MAP2K2	2	32-67	NM_030662	19
MET	2	66-102	NM_000245	7
MET	2	360-391	NM_000245	7
MET	11	799-837	NM_000245	7
MET	14	982-1009	NM_000245	7
MET	15	1063-1086	NM_000245	7
MET	16	1088-1113	NM_000245	7
MET	19	1229-1255	NM_000245	7
MTOR	30	1457-1489	NM_004958	1
MTOR	39	1789-1810	NM_004958	1
MTOR	40	1872-1904	NM_004958	1
MTOR	43	1999-2011	NM_004958	1
MTOR	43	1971-1979	NM_004958	1
MTOR	47	2187-2221	NM_004958	1
MTOR	53	2394-2434	NM_004958	1
NRAS	2	4-30	NM_002524	1
NRAS	3	43-68	NM_002524	1
NRAS	4	113-149	NM_002524	1
PDGFRA	12	552-583	NM_006206	4
PDGFRA	14	645-667	NM_006206	4
PDGFRA	18	820-853	NM_006206	4
PIK3CA	2	24-60	NM_006218	3
PIK3CA	2	79-113	NM_006218	3
PIK3CA	5	317-351	NM_006218	3
PIK3CA	6	354-377	NM_006218	3
PIK3CA	8	418-433	NM_006218	3
PIK3CA	8	450-468	NM_006218	3
PIK3CA	10	533-554	NM_006218	3

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PIK3CA	14	692-729	NM_006218	3
PIK3CA	19	899-923	NM_006218	3
PIK3CA	21	1018-1050	NM_006218	3
RAF1	7	246-273	NM_002880	3
RAF1	12	407-441	NM_002880	3
RET	10	609-626	NM_020630	10
RET	11	628-653	NM_020630	10
RET	13	763-785	NM_020630	10
RET	15	876-909	NM_020630	10
RET	16	911-923	NM_020630	10
ROS1	36	1942-1980	NM_002944	6
ROS1	38	2003-2036	NM_002944	6
SMO	6	392-418	NM_005631	7
SMO	8	454-488	NM_005631	7
SMO	9	512-542	NM_005631	7

**Copy Number Aberrations**

Gene	Accession	Chromosomal Location
ALK	NM_004304	2p23
AR	NM_000044	Xq12
BRAF	NM_004333	7q34
CCND1	NM_053056	11q13.3
CDK4	NM_000075	12q14
CDK6	NM_001259	7q21-22
EGFR	NM_005228	7p11
ERBB2	NM_004448	17q12
FGFR1	NM_023105	8p11
FGFR2	NM_000141	10q26
FGFR3	NM_000142	4p16
FGFR4	NM_002011	5q35
KIT	NM_000222	4q12
KRAS	NM_004985	12p12
MET	NM_000245	7q31
MYC	NM_002467	8q24
MYCN	NM_005378	2p24
PDGFRA	NM_006204	4q12
PIK3CA	NM_006218	3q26



**Title:** CMD Solid Tumour Service Users Guide**Fusion Genes**

Fusion Gene	Fusion	Exons	Cosmic Fusion number
ABL1	EML1-ABL1	E17A2	
AKT3	MAGI3-AKT3	M10A3	
ALK	ACTG2-ALK	A2A18	
ALK	EML4-ALK	E13A20	AB462411
ALK	EML4-ALK	E18A20	COSF487
ALK	EML4-ALK	E20A20	COSF409
ALK	EML4-ALK	E2A20	COSF478
ALK	EML4-ALK	E6A17	
ALK	EML4-ALK	E6A18	
ALK	EML4-ALK	E6A19	COSF1296
ALK	EML4-ALK	E6aA20	AB374361
ALK	GTF2IRD1-ALK	G7A20	
ALK	HIP1-ALK	H21A20	
ALK	HIP1-ALK	H28A20	
ALK	KIF5B-ALK	K15A20	COSF1381
ALK	KIF5B-ALK	K17A20	COSF1257
ALK	KIF5B-ALK	K24A20	COSF1058
ALK	KLC1-ALK	K9A20	COSF1276
ALK	MEMO1-ALK	M2A7	
ALK	STRN-ALK	S3A20	COSF1430
ALK	TFG-ALK	T4A20	COSF424
ALK	TFG-ALK	T5A20	COSF426
ALK	TFG-ALK	T6A20	COSF428
ALK	TPM1-ALK	T8A20	
ALK	TPM3-ALK	T7A20	
ALK	TPR-ALK	T15A20	
ALK	VCL-ALK	V16A20	COSF1057
ALK	A2M-ALK	A22A19	
ALK	ATIC-ALK	A7A20	
ALK	CARS-ALK	C17A20	
ALK	CLTC-ALK	C31A20	
ALK	DCTN1-ALK	D26A20	
ALK	EML4-ALK	E21A20	
ALK	RANBP2-ALK	R18A20	
ALK	SEC31L1_SEC31A-ALK	S21A20	
ALK	SEC31L1_SEC31A-ALK	S22A20	
ALK	TRAF1-ALK	T6A20	
ALK	TPM4-ALK	T7A20	
ALK	C2orf44-ALK	C4A20	

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ALK	EML4-ALK	E13A20	COSF1062
ALK	EML4-ALK	E14A20	COSF1064
ALK	EML4-ALK	E14A20	COSF477
ALK	EML4-ALK	E17A20	COSF1366
ALK	EML4-ALK	E17A20	COSF1367
ALK	EML4-ALK	E20A20	COSF730
ALK	EML4-ALK	E2A20	COSF479
ALK	EML4-ALK	E6bA20	AB374362
ALK	EML4-ALK	E7A20	
ALK	KIF5B-ALK	K15A20	COSF1060
ALK	NCOA1-ALK	N21A1	
ALK	EML4-ALK	E3p53insA20	
ALK	SMEK2-ALK	S9A2	
ALK	EML4-ALK	E15A20	COSF413
ALK	PRKAR1A-ALK	P2A20	
ALK	EML4-ALK	E6ins18A20	
ALK	EML4-ALK	E13ins90A20	
ALK	EML4-ALK	E14ins2del52A20	
ALK	EML4-ALK	E14ins124A20	
ALK	EML4-ALK	E14del36A20	
ALK	EML4-ALK	E17ins65A20	
ALK	EML4-ALK	E17ins68A20	
ALK	EML4-ALK	E17ins30A20_V8a	
ALK	CLIP4-ALK	C12A23	
BRAF	AKAP9-BRAF	A8B9	COSF1013.1
BRAF	CDC27-BRAF	C16B9	
BRAF	FAM131B-BRAF	F2B9	COSF1189
BRAF	FCHSD1-BRAF	F13B9	COSF404
BRAF	KIAA1549-BRAF	K16B10	COSF509
BRAF	KIAA1549-BRAF	K17B10	
BRAF	KIAA1549-BRAF	K18B9	
BRAF	PAPSS1-BRAF	P5B9	
BRAF	SLC45A3-BRAF	S1B8	COSF871
BRAF	SND1-BRAF	S16B9	
BRAF	TRIM24-BRAF	T9B9	
BRAF	KIAA1549-BRAF	K15B9	
BRAF	KIAA1549-BRAF	K15B11	
BRAF	TAX1BP1-BRAF	T8B11	
BRAF	AGTRAP-BRAF	A5B8	COSF828
EGFR	EGFR-EGFR	E1E8	
ERBB2	WIPF2-ERBB2	W1E4	

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ERG	SLC45A3-ERG	S1E4	COSF1138
ERG	TMPRSS2-ERG	T1E2	COSF23
ERG	TMPRSS2-ERG	T1E3	COSF24
ERG	TMPRSS2-ERG	T1E4	COSF38
ERG	TMPRSS2-ERG	T1E5	COSF26
ERG	TMPRSS2-ERG	T1E6	COSF36
ERG	TMPRSS2-ERG	T1EIIIc_4	
ERG	TMPRSS2-ERG	T2E2	COSF27
ERG	TMPRSS2-ERG	T2E4	COSF28
ERG	TMPRSS2-ERG	T2EIIIc_4	
ERG	TMPRSS2-ERG	T2E5	COSF29
ERG	TMPRSS2-ERG	T3E4	COSF30
ERG	TMPRSS2-ERG	T4E4	COSF18
ERG	TMPRSS2-ERG	T4E5	COSF17
ERG	TMPRSS2-ERG	T5E4	COSF16
ERG	TMPRSS2-ERG	T5E5	
ETV1	TMPRSS2-ETV1	T1E5	
ETV1	TMPRSS2-ETV1	T2E5	
ETV1	TMPRSS2-ETV1	T1E4	
ETV1	TMPRSS2-ETV1	T1bE4	
ETV4	TMPRSS2-ETV4	T1bE3	
ETV5	TMPRSS2-ETV5	T1E2	EU314929
ETV5	TMPRSS2-ETV5	T3E2	EU314930
ETV5	TMPRSS2-ETV5	T1bE2	
FGFR1	BAG4-FGFR1	B2F6	
FGFR1	ERLIN2-FGFR1	E8F2	
FGFR1	BAG4-FGFR1	B1F8	
FGFR1	FGFR1-TACC1	F17T7	
FGFR2	FGFR2-AFF3	F17A8	
FGFR2	FGFR2-BICC1	F17B2	
FGFR2	FGFR2-CASP7	F17C2	
FGFR2	FGFR2-CIT	F17C23	
FGFR2	SLC45A3-FGFR2	S1F1	
FGFR2	SLC45A3-FGFR2	S1F2	
FGFR2	FGFR2-KIAA1967_CCAR2	F17C4	
FGFR2	FGFR2-MGEA5	F17M12	
FGFR2	FGFR2-OFD1	F17O3	
FGFR2	FGFR2-TACC3	F17T11	
FGFR3	FGFR3-AES	F17A2	
FGFR3	FGFR3-BAIAP2L1	F17B2	COSF1347
FGFR3	FGFR3-ELAVL3	F17E2	

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FGFR3	FGFR3-TACC3	F15T11	
FGFR3	FGFR3-TACC3	F16T10	COSF1359
FGFR3	FGFR3-TACC3	F16T11	COSF1348
FGFR3	FGFR3-TACC3	F17T10	COSF1434
FGFR3	FGFR3-TACC3	F17T11	
FGFR3	FGFR3-TACC3	F17T5	
FGFR3	FGFR3-TACC3	F17T6	
FGFR3	FGFR3-TACC3	F17T8	
FGFR3	FGFR3-TACC3	F17T9	
FGFR3	FGFR3-TACC3	F17T13	
FGFR3	FGFR3-TACC3	F18T7	
FGFR3	FGFR3-TACC3	F14T11	
FGFR3	FGFR3-TACC3	F18T4and5	
FGFR3	FGFR3-TACC3	F18T10	
FGFR3	FGFR3-TACC3	F18T10	
FGFR3	FGFR3-TACC3	F18T11	
FGFR3	FGFR3-TACC3	TruncatedF17T4	
FGFR3	FGFR3-TACC3	F17T7	
FGFR3	FGFR3-TACC3	F17T10	
FGFR3	FGFR3-TACC3	F17T11	
FGFR3	FGFR3-TACC3	F17T11	
FGFR3	FGFR3-TACC3	F17intron17T4	
FGFR3	FGFR3-TACC3	F17Intron17T9	
MBIP	AXL-MBIP	A20M4	
MET	BAIAP2L1-MET	B9M15	
MET	C8orf34-MET	C2M15	
MET	CAPZA2-MET	C4M11	
MET	MET-MET	M13M15	
MET	OXR1-MET	O9M13	
MET	PTPRZ1-MET	P1M2	
MET	PTPRZ1-MET	P3M2	
MET	PTPRZ1-MET	P8M2	
MET	TFG-MET	T5M15	
MET	TPR-MET	T4M15	
NTRK1	NTRK1-DYNC2H1	N17D85	
NTRK1	MPRIP-NTRK1	M14N12	
NTRK1	MPRIP-NTRK1	M18N12	
NTRK1	MPRIP-NTRK1	M21N12	
NTRK1	SQSTM1-NTRK1	S5N10	
NTRK1	SSBP2-NTRK1	S12N12	
NTRK1	TFG-NTRK1	T6N10	

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NTRK1	TPM3-NTRK1	T7N10	COSF1318
NTRK1	TPR-NTRK1	T21N10	
NTRK1	BCAN-NTRK1	B13N11	
NTRK1	LMNA-NTRK1	L2N11	
NTRK1	NFASC-NTRK1	N20N10	
NTRK1	RNF213-NTRK1	R15N12	
NTRK1	CD74-NTRK1	C7N10	
NTRK1	CEL-NTRK1	C7N7	
NTRK1	IRF2BP2-NTRK1	I1N10	
NTRK1	TPR-NTRK1	T6N12	
NTRK1	TPR-NTRK1	T6N12	
NTRK1	TPR-NTRK1	T21N9	
NTRK2	AFAP1-NTRK2	A14N12	
NTRK2	AGBL4-NTRK2	A6N16	
NTRK2	NACC2-NTRK2	N4N13	
NTRK2	QKI-NTRK2	Q6N16	
NTRK2	SQSTM1-NTRK2	S5N17	
NTRK2	TRIM24-NTRK2	T12N15	
NTRK2	VCL-NTRK2	V16N12	
NTRK3	ETV6-NTRK3	E4N15	COSF823
NTRK3	ETV6-NTRK3	E5N15	COSF571
NTRK3	BTBD1-NTRK3	B4N14	
NTRK3	COX5A-NTRK3	C1N15	
NTRK3	ETV6-NTRK3	E4N14	
NTRK3	ETV6-NTRK3	E5N14	
PDGFRA	SCAF11-PDGFRA	S1P2	
PPARG	PAX8-PPARG	P10P2	COSF1219
PPARG	PAX8-PPARG	P7P2	COSF1223
PPARG	PAX8-PPARG	P8P2	COSF1215
PPARG	PAX8-PPARG	P9P2	COSF1217
PTPN3	ALK-PTPN3	A11P3	
RAF1	B4GALT1-RAF1	B1R8	
RAF1	ESRP1-RAF1	E13R6	COSF826
RET	CCDC6-RET	C1R12	COSF1271
RET	CUX1-RET	C10R12	
RET	ERC1_ELKS-RET	E11R12	COSF1508
RET	ERC1-RET	E12R12	
RET	ERC1-RET	E17R12	
RET	ERC1-RET	E7R12	
RET	FKBP15-RET	F25R12	
RET	GOLGA5-RET	G7R12	

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RET	HOOK3-RET	H11R12	
RET	KIAA1468-RET	K10R12	
RET	KIF5B-RET	K15R12	COSF1232
RET	KIF5B-RET	K16R12	COSF1230
RET	KIF5B-RET	K22R12	COSF1253
RET	KIF5B-RET	K23R12	COSF1234
RET	KIF5B-RET	K24R11	COSF1262
RET	KIF5B-RET	K24R8	COSF1236
RET	NCOA4-RET	N7R12	
RET	PCM1-RET	P29R12	
RET	PRKAR1A-RET	P7R12	
RET	TBL1XR1-RET	T9R12	
RET	TRIM27-RET	T3R12	
RET	TRIM33-RET	T16R12	
RET	ACBD5-RET	A11R12	
RET	AFAP1-RET	A3R12	
RET	AKAP13-RET	A35R12	
RET	NCOA4_ELE1-RET	E6R12	
RET	SPECC1L-RET	S10R12	
RET	KTN1-RET	K29R12	COSF1513
RET	RUFY2-RET	R9R12	
RET	KIF5B-RET	K15R11	COSF1255
RET	SPECC1L-RET	S10R11	
RET	TBL1XR1-RET	T9R11	
RET	TRIM24-RET	T9R12	
RET	AKAP13-RET	A36R12	
RET	CCDC6-RET	C1R13	
RET	CCDC6-RET	C2R12	
RET	CCDC6-RET	C8R11	
RET	CCDC6-RET	C8R12	
RET	CCDC6-RET	C1R12	
RET	CCDC6-RET	C1R11	
RET	CCDC6-RET	C1R11	
ROS1	CD74-ROS1	C6R32	COSF1202
ROS1	CD74-ROS1	C6R34	COSF1200
ROS1	CEP85L-ROS1	C8R36	
ROS1	EZR-ROS1	E10R34	COSF1267
ROS1	GOPC-ROS1	G4R36	COSF1188
ROS1	GOPC-ROS1	G8R35	COSF1139
ROS1	LRIG3-ROS1	L16R35	COSF1269
ROS1	SDC4-ROS1	S2R32	COSF1265

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ROS1	SDC4-ROS1	S2R34	
ROS1	SDC4-ROS1	S4R32	COSF1278
ROS1	SDC4-ROS1	S4R34	COSF1280
ROS1	SLC34A2-ROS1	S4R32	COSF1197
ROS1	SLC34A2-ROS1	S4R34	COSF1198
ROS1	CLTC-ROS1	C31R35	
ROS1	ERC1-ROS1	E11R36	
ROS1	HLA_A-ROS1	H7R34	
ROS1	KIAA1598-ROS1	K11R36	
ROS1	MYO5A-ROS1	M23R35	
ROS1	PPFIBP1-ROS1	P9R35	
ROS1	PWWP2A-ROS1	P1R36	
ROS1	TPM3-ROS1	T3R36	
ROS1	ZCCHC8-ROS1	Z2R36	
ROS1	TFG-ROS1	T4R35	
ROS1	CD74-ROS1	C6R35	
ROS1	EZR-ROS1	E10R35	
ROS1	MSN-ROS1	M9R34	
ROS1	CCDC6-ROS1	C5R35	
ROS1	CD74-ROS1	C4R33	
ROS1	KDEL2-ROS1	K5R35	
ROS1	SLC34A2-ROS1	S13R32	COSF1259
ROS1	SLC34A2-ROS1	S13R34	COSF1261
ROS1	SLC34A2-ROS1	S13R36	
ROS1	TPM3-ROS1	T7R35	COSF1273
ROS1	CLIP1-ROS1	C19R36	
ROS1	KDEL2-ROS1	K5Rintron34	

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