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T. Spence Ontario Cancer Institute University of Toronto

N. Stickle Ontario Cancer Institute University of Toronto

C. Yu Ontario Cancer Institute University of Toronto

H. Chow Ontario Cancer Institute University of Toronto

H. Feilotter *Kingston Health Sciences Centre* 

See next page for additional authors

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### Authors

T. Spence, N. Stickle, C. Yu, H. Chow, H. Feilotter, B. Lo, E. McCready, B. Sadikovic, L. L. Siu, P. L. Bedard, and Tracy L. Stockley

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# Inter-laboratory proficiency testing scheme for tumour next-generation sequencing in Ontario: a pilot study

T. Spence PhD,\* N. Stickle,\* C. Yu CCRP,\* H. Chow,\* H. Feilotter PhD,<sup>†</sup> B. Lo MD PhD,<sup>‡</sup> E. McCready PhD,<sup>§</sup> B. Sadikovic PhD,<sup>||</sup> L.L. Siu MD,\* P.L. Bedard MD,\* and T.L. Stockley PhD\*

### ABSTRACT

**Background** A pilot inter-laboratory proficiency scheme for 5 Ontario clinical laboratories testing tumour samples for the Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) study was undertaken to assess proficiency in the identification and reporting of next-generation sequencing (NGS) test results in solid tumour testing from archival formalin-fixed, paraffin-embedded (FFPE) tissue.

**Methods** One laboratory served as the reference centre and provided samples to 4 participating laboratories. An analyte-based approach was applied: each participating laboratory received 10 FFPE tissue specimens profiled at the reference centre, with tumour site and histology provided. Laboratories performed testing per their standard NGS tumour test protocols. Items returned for assessment included genes and variants that would be typically reported in routine clinical testing and variant call format (VCF) files to allow for assessment of NGS technical quality.

**Results** Two main aspects were assessed:

- Technical quality and accuracy of identification of exonic variants
- Site-specific reporting practices

Technical assessment included evaluation of exonic variant identification, quality assessment of the vcF files to evaluate base calling, variant allele frequency, and depth of coverage for all exonic variants. Concordance at 100% was observed from all sites in the technical identification of 98 exonic variants across the 10 cases. Variability between laboratories in the choice of variants considered clinically reportable was significant. Of the 38 variants reported as clinically relevant by at least 1 site, only 3 variants were concordantly reported by all participating centres as clinically relevant.

**Conclusions** Although excellent technical concordance for NGS tumour profiling was observed across participating institutions, differences in the reporting of clinically relevant variants were observed, highlighting reporting as a gap where consensus on the part of Ontario laboratories is needed.

**Key Words** External quality assessment, inter-laboratory comparison, next-generation sequencing, tumour molecular profiling

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### INTRODUCTION

Next-generation sequencing (NGS) for molecular profiling of solid tumours is rapidly becoming standard-of-care

testing in molecular laboratories in Canada because of the simultaneous yield of clinically useful genetic information, benefit of tissue preservation by avoiding sequential testing, and declining cost of NGS equipment and operations.

Correspondence to: Tracy L. Stockley, 11E-418 Eaton Wing, 200 Elizabeth Street, Toronto, Ontario M5G 2C4. E-mail: tracy.stockley@uhn.ca **DOI:** https://doi.org/10.3747/co.26.5379 Supplemental material available at http://www.current-oncology.com

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Proficiency testing (PT) schemes (also known as external quality assessment if offered by an external body), in which laboratories are assessed on blinded analysis of samples with known results, is an integral part of ensuring quality of NGS and other molecular tests<sup>1,2</sup>. However, a national PT scheme for molecular pathology laboratory testing (using NGS or any method) does not exist in Canada, likely because of the effort of establishing a scheme potentially subscribed to by only a small number of Canadian laboratories, and because of the effort of sample acquisition and PT assessment. In Ontario, all licensed and accredited clinical laboratories offering testing for patient care are required to participate in PT as mandated by the provincial accreditation body (Institute for Quality Management in Healthcare), based on the International Organization for Standardization 15189 standard. The Institute for Quality Management in Healthcare requires that, to maintain accreditation, clinical laboratories complete PT for 4 samples within a 12-month period for each clinical test. In the absence of a PT program offered by a Canadian organization for tumour molecular profiling, accredited laboratories must identify suitable alternatives, such as international PT programs or informal sample exchange, to meet the Ontario requirements.

A key consideration in the design of a PT scheme for tumour molecular profiling is the selection of sample source material. To perform both pre-analytic and analytic comparisons of laboratory proficiency, the optimal material is formalin-fixed, paraffin-embedded (FFPE) tumour tissue, because that sample source allows for an assessment of pre-analytic variables. However, obtaining FFPE tumour tissue for PT is often hampered by a small tumour amount and suboptimal quality of the available clinically relevant material. Tumour heterogeneity can also lead to potential differences in results. Although tracking of FFPE sections sent to participating laboratories is possible, that approach does not ameliorate the risk of error. An alternative approach is to use DNA extracted from FFPE tissue<sup>3</sup>, with the inherent limitation that use of DNA prevents identification of any potential issues related to the pre-analytic phase. Other source material could also be used, such as cell lines embedded in paraffin or synthetic DNA controls, each with its own limitations. Any of those sample issues might lead to inappropriate discrepancies in PT testing results originating solely in the material sent within the PT scheme.

The other significant aspect in PT schemes is whether the scheme assesses only the technical aspects (for example, by requesting return of variants only) or also assesses the post-analytic clinical interpretation and reporting aspects (for example, by requesting that variant interpretations or mock clinical reports be returned). For testing of solid tumours, general guidelines about reporting aspects for laboratory tests are available<sup>4</sup>; however, those guidelines might not be sufficiently detailed for PT schemes, which are often specific to a gene or a disease indication. Proficiency testing schemes might also request return of various types of data-for example, only the Human Genome Variation Society nomenclature for identified variants, or variants plus data files for data quality analysis, which typically compares data across laboratories rather than scoring based on an evaluative scheme.

In the present study, a pilot PT scheme (Figure 1) was implemented for Ontario laboratories participating in the Ontario-Wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) study, which is an ongoing prospective trial open at 5 academic cancer centres. The trial aims to enable genotype–drug matching through somatic NGS testing of FFPE solid tumour tissue from patients with advanced cancer and to facilitate clinical and genomic data-sharing. The PT scheme was designed as a pre- to post-analytic scheme, with dissemination of FFPE tumour material and return of variants, variant call format (VCF) files, and information about clinically reportable genes and variants. We highlight the successes and challenges of that approach to PT schemes for solid tumour molecular profiling in the Ontario context.

### **METHODS**

### **Participating Laboratories**

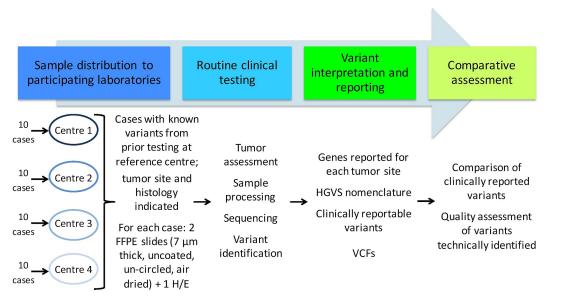
Participating laboratories included the Princess Margaret Cancer Centre (PMCC), University Health Network, Toronto (which acted as the reference site for source materials and result evaluations); the Juravinski Cancer Centre (JCC), Hamilton; the London Health Sciences Centre (LHSC), London; The Ottawa Hospital (TOH), Ottawa; and the Kingston Health Sciences Centre (KHSC), Kingston. A laboratory director from each site was involved in the study design.

### **Tumour Tissue Specimens**

From a cohort of FFPE tissues banked at the reference laboratory, 10 FFPE specimens of tumour tissue were chosen from resections in patients enrolled in the OCTANE trial (NCT02906943 at https://ClinicalTrials.gov/) with approval from the Ontario Cancer Research Ethics Board (ID: 16-018). All 10 specimens had previously been tested by NGs at the reference laboratory. Specimens were chosen so as to provide to each of the 4 participating sites a variety of genes and variants, and to meet these additional criteria: tumour cellularity greater than or equal to 20% in the tumour area, and sufficient FFPE material to provide 2 unstained sections at 7 µm thickness and 1 slide stained with hematoxylin and eosin. Sections were numbered as cut, and the section numbers distributed to each laboratory were recorded to enable tracking of the location within the tumour block in case of tumour heterogeneity for variants. Unstained and uncircled sections were provided on air-dried, uncoated slides. Tumour site and histology as determined by a study pathologist at the reference site were also provided to the participating laboratories.

### Molecular Profiling Assays

The participating laboratories used 2 NGS panels in testing DNA samples. The reference laboratory (PMCC) used a custom hybridization capture NGS panel of 555 cancer-related genes [UHN Hi5 panel (SureSelect: Agilent, Santa Clara, CA, U.S.A.)] sequenced on the NextSeq platform (Illumina, San Diego, CA, U.S.A.). The other 4 participating laboratories (JCC, LHSC, TOH, KHSC) used a commercial amplicon-based hotspot panel that included regions of 50 genes (Ion AmpliSeq Cancer Hotspot Panel v2: Thermo Fisher, Waltham, MA, U.S.A.) and was sequenced on the



**FIGURE 1** Flow-chart depicting the pilot proficiency-testing workflow. Ten formalin-fixed, paraffin-embedded (FFPE) tumour proficiency testing cases with known variants from prior testing at the reference centre were distributed to each of the 4 participating laboratories, with tumour site and histology indicated. Cases were processed at participating centres per routine clinical testing for the Ontario-wide Cancer Targeted Nucleic Acid Evaluation (OCTANE) study. Participating centres were requested to provide a list of the genes reported for each tumour site, clinically reportable variants, and variant call format (VCF) files. Comparative assessment was performed to evaluate concordance in the technical identification of variants and concordance in the clinically reported and annotated variants. H/E = hematoxylin and eosin stained; HGVS = Human Genome Variation Society.

Ion Torrent PGM platform (Thermo Fisher) at each site. Those 4 laboratories were accredited by the Ontario provincial laboratory accreditation body (the Institute for Quality Management in Healthcare), and the remaining laboratory (PMCC) was accredited by the College of American Pathologists (CAP) and was certified as meeting the U.S. Clinical Laboratory Improvement Amendments. Laboratories were instructed to not communicate results with other laboratories and to treat the samples in a manner similar to other clinical samples as much as possible for the entire workflow.

### Variant Assessment and Reporting

For each of the 10 specimens, participating laboratories were requested to return the following information to the reference laboratory within 4 weeks (supplemental Appendix 1):

- A list of genes for each tumour site the laboratory would consider to be clinically reportable from the panel in use
- The variants identified in each of the 10 specimens that the laboratory considered to be clinically reportable, with variant interpretations
- A list of variants that met laboratory-defined minimum technical quality metrics for high-quality variants (that is, all high-quality variants whether considered clinically reportable or not)
- The vCF files from the relevant NGS panel test at each site

The кнsc provided vcF files that were pre-filtered according to their current laboratory practice; the JCC, тон, and LHSC provided unfiltered vcF files. Clinically reportable variants were defined as variants that would routinely be reported based on the clinical reporting practices for the octane study at that laboratory. Variant interpretations were requested to be performed and returned according to each laboratory's typical process for the octane study. Laboratories were requested to include Human Genome Variation Society nomenclature and any other nomenclature system typically used for reports generated for the octane study.

### Assessment of Technical and Reporting Performance

A comparative analysis was conducted to assess concordance in the variant information returned from each participating site with the variants identified by the reference site. Because the reference site used different NGS chemistry, analyses included assessment of concordance between the participating sites, but discordance with the reference laboratory results. That approach was instituted to rule out the bias of considering the reference laboratory results to be "true."

Variants were assessed by the accuracy with which reported variants were identified, including correct Human Genome Variation Society nomenclature. Technical quality metrics were assessed using the vcr files and BEDTools (version 2.23.0)<sup>5</sup>, with an intersection browser extensible data file created to identify overlapping regions in the UHN Hi5 panel and the Ion AmpliSeq Cancer Hotspot Panel v2, and to identify common and unique variants in the reference laboratory dataset and in each of the datasets from the 4 participating laboratories.

To assess reporting, the genes and variants that each laboratory provided as being clinically reportable were manually compared.

### RESULTS

### **Reportable Genes by Tumour Site**

Participating laboratories provided the list of genes typically reported clinically at their institution for each tumour site in the PT specimens, per their usual practice within the octane study. The list of reportable genes for each tumour site differed significantly between the participating centres (Table I). Of the participating laboratories, 2 chose to report on all genes on their panel, and 1 elected to report only variants in genes that were routinely reported in clinical practice at their institution, regardless of tumour type.

## Comparison of Base Calling and Quality Assessment of Raw Data

An analysis of the agreement in technical detection of variants identified in the vcF files for each case demonstrated 100% concordance (98 of 98 variants) in the identification of exonic variants from all sites for the 10 cases (Table II). Of the 98 exonic variants detected, a subset was identified below the lower variant allele frequency (vAF) and quality thresholds defined for PT evaluation—that is, less than 5% vAF and less than  $100 \times$  (PMCC) or  $500 \times$  (JCC, LHSC, TOH, KHSC) coverage. Of those low-vAF or low-coverage variants, none was considered clinically reportable by more than 1 laboratory.

 TABLE I
 List of genes that each participating laboratory would consider to be reportable for each tumour type included within the proficiency-testing specimens

Specimen ID	Tumour site and classification	Laboratory ID	Genes reported <sup>a</sup>
1	Melanoma		
	Melanoma	1	BAP1, BRAF, KIT, HRAS, NRAS
		2	All genes on panel
		3	BRAF, NRAS
		4	Not provided
		5	All genes on panel
2	Gastrointestinal cancer		
	Colorectal adenocarcinoma	1	BRAF, HER2/ERBB2, IDH1, IDH2, KRAS, NRAS, PIK3CA
		2	All genes on panel
		3	BRAF, KRAS, NRAS
		4	Not provided
		5	All genes on panel
3	Gynecologic cancer		
	Low-grade ovarian serous carcinoma	1	BRCA1, BRCA2, TP53, KRAS, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel
4	Gynecologic cancer		
	High–grade ovarian serous carcinoma	1	BRCA1, BRCA2, TP53, KRAS, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel
5	Liver cancer		
	Adenocarcinoma	1	BRAF, HER2/ERBB2, IDH1, IDH2, KRAS, NRAS, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel
6	Head-and-neck cancer		
	Parathyroid carcinoma	1	BRAF, EGFR, EZH2, KIT, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel

Specimen ID	Tumour site and classification	Laboratory ID	Genes reported <sup>a</sup>
7	Lung cancer		
	Adenocarcinoma	1	BRAF, EGFR, HER2/ERBB2, KRAS, MET, TP53
		2	All genes on panel
		3	BRAF, EGFR, KRAS
		4	Not provided
		5	All genes on panel
	Gynecologic cancer		
	High-grade ovarian serous carcinoma	1	BRCA1, BRCA2, TP53, KRAS, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel
1	Gynecologic cancer		
	High-grade ovarian serous carcinoma	1	BRCA1, BRCA2, TP53, KRAS, PIK3CA
		2	All genes on panel
		3	Genes not reported for this site
		4	Not provided
		5	All genes on panel
0	Lung cancer		
	Squamous cell carcinoma	1	BRAF, EGFR, HER2/ERBB2, KRAS, MET, TP53
		2	All genes on panel
		3	BRAF, EGFR, KRAS
		4	Not provided
		5	All genes on panel

### TABLE I Continued

<sup>a</sup> See Appendix A for a complete list of genes on the next-generation sequencing panels used in the present study.

### Variants Considered Clinically Reportable

The PT results provided by each institution included a list of variants in each case that were considered clinically reportable per routine practice in the OCTANE study (Table III). A high degree of variability in the variants considered clinically reportable was also observed, with only 3 variants from the 10 cases being concordantly reported by all 5 participating centres. Concordant reporting of 5 variants by 4 or more centres and of 10 variants by 3 or more centres was observed.

### **Interpretation of Clinically Reportable Variants**

Variants considered clinically reportable were classified by 4 of the laboratories using a published somatic variant classification scheme. The joint guideline from the Association for Molecular Pathology (AMP), the American Society of Clinical Oncology (Asco), and CAP (AMP/ASCO/ CAP) published by Li *et al.*<sup>6</sup> was applied by 3 laboratories, and the Sukhai *et al.*<sup>7</sup> guideline was used by 1 laboratory. Significant variability was observed in the classifications provided for specific variants (Table III). For example, one laboratory indicated that the *TP53* p.Leu252del variant identified in case 8 was a tier II variant, while another indicated that the same variant was a tier III variant. That same variant was classified as class 3A by a 3rd site and was not clinically reported by the remaining 2 laboratories. Similarly, the *TP53* p.Ser127Phe variant identified in case 1 was reported as tier 11 by 1 site and as tier 111 by 1, with the other 3 sites not reporting it. Furthermore, 1 site chose to include variants classified as tier 111 or 1v according to the AMP/ASCO/CAP guideline as clinically reportable.

### DISCUSSION

The present study set out to evaluate the performance of solid tumour molecular profiling at the 5 Ontario sites (JCC, LHSC, TOH, KHSC, and PMCC) that provide NGS molecular profiling for the OCTANE study. An analyte-based PT approach was used, with FFPE tumour tissue being sent out, and information related to variants considered clinically relevant being returned, in an end-to-end evaluation of laboratory performance.

Although the use of FFPE tissue allows for an evaluation of the pre-analytic phase, it can also adversely affect other aspects of the PT scheme. At the reference laboratory, it was difficult to source sufficient FFPE tumour tissue material meeting all parameters specified in the Methods section for distribution to the 4 participant sites. Of the 10 samples,

Autom         Control         Control <th< th=""><th>Specimen</th><th>Gene</th><th>Variant type</th><th>Genomic</th><th>Variant</th><th></th><th>Labo</th><th>Laboratory ID<sup>a</sup></th><th>ΙD<sup>a</sup></th><th></th></th<>	Specimen	Gene	Variant type	Genomic	Variant		Labo	Laboratory ID <sup>a</sup>	ΙD <sup>a</sup>	
Nonsynonymous SNV         chri 11526528         NRASMM 002524:eeon13:c.C181Ap.Q61K         X         X           Nonsynonymous SNV         chri 53593244         KTB-ML 00023:3:eeon11:c.A1161;Q.Q47H         X         X           Nonsynonymous SNV         chri 55594294         TP53.3.ML 00023:4:eeon14:c.C1167,p.P567         X         X           Nonsynonymous SNV         chri 57559472         TP53.3.ML 0003:4:eeon4:c.C135Ap.1611         X         X           Synonymous SNV         chri 77559472         TP53.3.ML 0003:4:eeon4:c.C135Ap.16191         X         X           Synonymous SNV         chri 77559472         TP53.3.ML 0003:4:eeon4:c.C135Ap.114911         X         X           Synonymous SNV         chri 17559412         PCRNML 0003:4:eeon14:c.C195Ap.114911         X         X           Synonymous SNV         chri 154124         RRSNML 0003:4:eeon20:c.C135Ap.114911         X         X           Synonymous SNV         chri 1534242         HRASNML 0003:4:eeon20:c.C135Ap.114911         X         X           Nonsynonymous SNV         chri 1534242         RRSNML 0003:4:eeon4:c.C135Ap.114911         X         X           Nonsynonymous SNV         chri 7:53942         RRSNML 0003:4:eeon4:c.C135Ap.114911         X         X           Nonsynonymous SNV         chri 7:537912         TP53.NML 0003:4:eeon4:c.C13				cooluliates		-	2	3	4	Ŋ
Nonsynonymous SNV         chris11236528         NRASIML 002324scon3t.C181Ap.Q6IK         X         X           Nonsynonymous SNV         chris1557344         KENML00234scon1t.c.A1162.Q412H         X         X           Nonsynonymous SNV         chris557345         TF33.1ML 000344scon5t.C136Gp.F31F         X         X           Nonsynonymous SNV         chris573445         TF33.1ML 000344scon5t.C136Gp.F31F         X         X           Synonymous SNV         chris5111275769         FGRN.ML 00034scon5t.C136Gp.F37F         X         X           Synonymous SNV         chris5111275769         FGRN.ML 00034scon5t.C136Gp.F37F         X         X           Synonymous SNV         chris511275769         FGRN.ML 00034scon5t.C136Gp.F37F         X         X           Synonymous SNV         chris511275769         FGRN.ML 00034scon5t.C136Gp.F37F         X         X           Synonymous SNV         chris512127569         FGRN.ML 00034scon5t.C136Gp.F27H         X         X           Nonsynonymous SNV         chris512127569         FGRN.ML 000354scon6t.C136Gp.F27H         X         X           Nonsynonymous SNV         chris537234         RRASN.ML 00142scon4t.C.C136Gp.F27H         X         X           Nonsynonymous SNV         chris537234         RRASN.ML 000233scon11t.C.A1416Fp.Q472H         X         <	Melanoma									
Nonsynonymous SNV         drid:5593464         KIENM_000222:exon116.c/A16116.p.Q75H         X         X           Nonsynonymous SNV         drid:5597344         TF33.NL_000546exon15.c.C1367.p.75T         X         X           Nonsynonymous SNV         drid:7575646         TF33.NL_000546exon15.c.C1367.p.75T         X         X           Synonymous SNV         drid:7573405         FGR3.NL_000346exon15.c.C1367.p.75T         X         X           Synonymous SNV         drid:5111050         PDGFRAML_002306.exon12.c.A1701G.p.7567P         X         X           Synonymous SNV         drid:5141050         PDGFRAML_002306.exon12.c.A1701G.p.756P         X         X           Synonymous SNV         drid:1243923         REFNM_0003348exon16.c.C.41971G.p.1761         X         X           Synonymous SNV         dri1:33422         PRASNM_003546exon35.c.C.3167.p.472H         X         X           Nonsynonymues SNV         drid:5371210         TF33.NL_000346exon4.c.C.1316.p.472H         X         X           Nonsynonymues SNV         drid:531.p.17569         RRASNM_003546exon4.c.C.1316.p.472H         X         X           Nonsynonymues SNV         drid:531.p.17561         RRASNM_00346exon4.c.C.1316.p.472H         X         X           Synonymous SNV         drid:531.p.17556         APC:NM_000346exon4.c.C.1316.p.472H </td <td></td> <td>NRAS</td> <td>Nonsynonymous SNV</td> <td>chr1:115256528</td> <td>NRAS:NM_002524:exon3:c.C181A:p.Q61K</td> <td>×</td> <td>×</td> <td>×</td> <td>×</td> <td>×</td>		NRAS	Nonsynonymous SNV	chr1:115256528	NRAS:NM_002524:exon3:c.C181A:p.Q61K	×	×	×	×	×
Nonsynonymous SNV         chris5392974         KDR:NM.002233:scon11c.A1416Fp.Q472H         X         X           Nonsynonymous SNV         chri5759456         TP33:NM.000546:exon5t.C.G1967;p71F         X         X           Synonymous SNV         chri5759420         TP33:NM.000546:exon12c.A1701Gp.P567P         X         X           Synonymous SNV         chri5112175769         PDCFRA:NM.000206:exon12c.A1701Gp.P567P         X         X           Synonymous SNV         chri5112175769         PDCFRA:NM.000206:exon12c.A1701Gp.P567P         X         X           Synonymous SNV         chri512127569         PDCFRA:NM.000506:exon12c.A1701Gp.P567P         X         X           Synonymous SNV         chri535249063         EGFRA:NM.000506:exon12c.A1701Gp.P37FP         X         X           Synonymous SNV         chri1535421         HRASNM_00536:exon12c.C1816/p.071FP         X         X           Nonsynonymous SNV         chr15757120         TF33.NM_00054:exon2c.C1316/p.072FF         X         X           Nonsynonymous SNV         chr157577120         TF33.NM_00034:exon4c.C1316/p.073FF         X         X           Nonsynonymous SNV         chr17757974         TF33.NM_00034:exon4c.C1316/p.073FF         X         X           Synonymous SNV         chr17757574         TF33.NM_00034:exon4c.C1316/p.072FF		KIT	Nonsynonymous SNV	chr4:55593464	KIT:NM_000222:exon10:c.A1621C:p.M541L	×	×	×	×	×
Norsynonymous SNV         chr17/578346         TF33:NM_000546:exon5:c.C.B0Tp.512F         X         X           Norsynonymous SNV         chr17/57942         TF93:NM_000546:exon12:c.G1761P567P         X         X           Synonymous SNV         chr17:5734165         PDGRA:NM_000546:exon12:c.G1761P567P         X         X           Synonymous SNV         chr13:1121756         APC:NM_0003546:exon12:c.G1761A757P         X         X           Synonymous SNV         chr13:33422         APC:NM_0003546:exon12:c.G1761A757P         X         X           Synonymous SNV         chr13:33422         APC:NM_0003746:exon12:c.G1761A757P         X         X           Nonsynonymous SNV         chr13:33422         APC:NM_0003745:exon13:c.G2307Fp.1769L         X         X           Nonsynonymous SNV         chr13:537272         RFI:NM_000345:exon13:c.G161A77H         X         X           Nonsynonymous SNV         chr13:537274         RS:NM_000346:exon14:c.G16747H         X         X           Nonsynonymous SNV         chr13:53743         RFI:NM_000346:exon14:c.G16747H         X         X           Nonsynonymous SNV         chr13:53742         RS:NM_000346:exon14:c.G16747AH         X         X           Synonymous SNV         chr13:575496         r1753:NM_000034:exon14:c.G16747AH         X         X <td></td> <td>KDR</td> <td>Nonsynonymous SNV</td> <td>chr4:55972974</td> <td>KDR:NM_002253:exon11:c.A1416T;p.Q472H</td> <td>×</td> <td>×</td> <td>×</td> <td>×</td> <td><math>\times</math></td>		KDR	Nonsynonymous SNV	chr4:55972974	KDR:NM_002253:exon11:c.A1416T;p.Q472H	×	×	×	×	$\times$
Nonsynonymous SNV         chr1:3757942         TP33:NM_000346exon4c.C115Gp.PZR         Yb         X           Synonymous SNV         chr4:1607694         FGRR:NM_000142-exon14c.C1953Ap.TG1T         X         X           Synonymous SNV         chr4:161764         PDCRRANM_000206exon12c.C1901Ap7617         X         X           Synonymous SNV         chr1:1217569         PCRN.L000038exon16c.C4479Ap.T1493T         X         X           Synonymous SNV         chr1:1317542         PRSNM_005248exon15c.C4479Ap.T1493T         X         X           Synonymous SNV         chr1:534242         PRSNM_005343exon15c.C437Ap.T691         X         X           Nonsynonymous SNV         chr1:57712         PRSNM_005348exon2c.C181Cp.H27H         X         X           Nonsynonymous SNV         chr1:57712         TF33.NM_00546exon4c.C15G.P72H         X         X           Nonsynonymous SNV         chr1:57712         TF33.NM_00546exon4c.C15G.P72H         X         X           Synonymous SNV         chr1:117757         APC.NM_00038exon16c.C4479Ap.T1491         X         X           Synonymous SNV         chr1:1317569         APC.NM_00038exon16c.C4479Ap.T1491         X         X           Synonymous SNV         chr1:1317569         APC.NM_00038exon16c.C4479Ap.T1491         X         X		TP53	Nonsynonymous SNV	chr17:7578546	TP53:NM_000546:exon5:c.C380T;p.S127F	×	×	×	×	×
Synonymous SNV         drk1807894         FGR3.NM_000142:exon14:cC1953Ap.T6517         X         X           Synonymous SNV         drk3511050         PDGFRANM_006206:exon12:cC4479Ap.T14931         X         X           Synonymous SNV         drk15112175769         APC.NM_00028:exon16:c.C4479Ap.T14931         X         X           Synonymous SNV         drk1534242         HRSNM_00338:exon15:c.C2307Fp.17691         X         X           Synonymous SNV         drk11534242         HRSNM_00334:exon2:c.G35Gp.G12A         X         X           Nonsynonymous SNV         drk115537242         TRSNM_0034:exon1:c.G1479Ap1         X         X           Nonsynonymous SNV         drk11553742         TRSNM_00034:exon1:c.G1479Ap1         X         X           Nonsynonymous SNV         drk1755745         APC.NM_00034:exon1:c.C1495Ap1274         X         X           Synonymous SNV         drk1755742         TP33.NM_00034:exon1:c.C1493Ap1274         X         X           Synonymous SNV         drk1755742         TP33.NM_00034:exon1:c.C1493Ap1274         X         X           Synonymous SNV         drk1755742         TP33.NM_00034:exon1:c.C1933Ap16511         X         X           Synonymous SNV         drk1755743         PCSNM_00033:exon1:c.C193Ap1714931         X         X		TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	чX	×	×	×	×
Synonymous SNV         chris5141050         PDCFRANM_006206:exon12:c.A1701G;p767P         X         X           Synonymous SNV         chr5111275769         APC:NM_000328:exon12:c.C13701G;p7570         X         X           Synonymous SNV         chr5112175769         APC:NM_00038:exon12:c.C13071p.1561         X         X           Synonymous SNV         chr10:43613843         RET:NM_00338:exon13:c.C33071p.1561         X         X           Synonymous SNV         chr11:53424         NRAS:NM_003343:exon12:c.C131Cp.H27H         X         X           Nonsynonymous SNV         chr11:53424         KRS:NM_003343:exon2:c.C33Cp.G12A         X         X           Nonsynonymous SNV         chr17:7579472         TP33:NM_000546:exon4:c.C115G;p.P74H         X         X           Nonsynonymous SNV         chr17:757472         TP33:NM_000546:exon4:c.C115G;p.P74H         X         X           Nonsynonymous SNV         chr17:757472         TP33:NM_000546:exon4:c.C115G;p.P74H         X         X           Synonymous SNV         chr17:757472         TP33:NM_000546:exon4:c.C116G;p.P74H         X         X           Synonymous SNV         chr17:75741         TP33:NM_000546:exon4:c.C116G;p.P74H         X         X           Synonymous SNV         chr3:112175769         TP33:NM_000346:exon4:c.C116G;p.P73R         X<		FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	<sup>d</sup> X	×	×	×
Synonymous SNV         dh5:112175769         APC:NM_00038:exon16c.Cd479Ap.T1493T         X         X           Synonymous SNV         chr5:5249063         EGR:NM_005228:exon26c.C361Ap.Q787Q         X         X*           Synonymous SNV         chr1:534242         HRAS:NM_005238:exon26c.C361Ap.Q787Q         X         X*           Synonymous SNV         chr1:534242         HRAS:NM_0033360:exon26c.C367C.pG12A         X         X*           Nonsynonymous SNV         chr1:53922974         KRS:NM_002354:exon13:c.C357C.pG12A         X         X*           Nonsynonymous SNV         chr1:5757120         TP33:NM_000546:exon3cc.G385Ap.G12A         X         X*           Nonsynonymous SNV         chr1:7757472         TP33:NM_000546:exon4c.C15G.p72R         X         X*           Synonymous SNV         chr1:7757472         TP33:NM_000546:exon4c.C15G.p72R         X         X*           Synonymous SNV         chr1:7757472         TP33:NM_000546:exon4c.C15G.p72R         X         X*           Synonymous SNV         chr1:775742         TP33:NM_000546:exon4c.C15G.p74P1         X         X*           Synonymous SNV         chr3:11217576         APC:NM_00038:exon16:c.C4195Ap.T1493T         X         X*           Synonymous SNV         chr3:11217576         APC:NM_000038:exon14:c.C15G.p7Ap.T1493T         X		PDCFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×	×
Synonymous SNV         ch7:55249063         EGR:NM_00528:exon20cc C2361Ap.Q787Q         X         X           Synonymous SNV         chr11:53424         HRS:NM_005343:exon13:c.C2307Fp.L769L         X         X           Synonymous SNV         chr11:53424         HRS:NM_005343:exon13:c.C2307Fp.L769L         X         X           Nonsynonymous SNV         chr11:53424         HRS:NM_00054:exon13:c.C1307Fp.L769L         X         X           Nonsynonymous SNV         chr17:7577120         TP53:NM_00054:exon14:c.C115G.p.P2R         X         X           Nonsynonymous SNV         chr17:7577120         TP53:NM_00054:exon14:c.C115G.p.P2R         X         X           Synonymous SNV         chr3:1807894         FGR:NM_00038-exon16:c.C115G.p.P2R         X         X           Synonymous SNV         chr3:112175769         APC:NM_00038-exon16:c.C115G.p.P2R         X         X           Synonymous SNV         chr3:51141050         PDGFRA:NM_00038-exon14:c.C115G.p.P2R         X         X           Synonymous SNV         chr3:112175769         APC:NM_00038-exon14:c.C115G.p.P2R         X         X           Synonymous SNV         chr3:51141050         PDGFRA:NM_0052.exon13:c.C114937         X         X           Synonymous SNV         chr3:51141050         PDGFRA:NM_0052.exon13:c.C156.p.P2R         X		APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×	×	×	×	×
Synonymaus SNV         dr/10:43613843         RETNM_020975:exon13:c.C2307Fp.1769L         X         X           Synonymaus SNV         dr/11:534242         HRASINM_0005343:exon2:c.G356;p.G12A         X         X           Nonsynonymous SNV         dr/12:23390280         KRASINM_003340:exon2:c.G356;p.G12A         X         X           Nonsynonymous SNV         dr/17:757912         TP53:NM_000546:exon11:c.A14167;p.Q472H         X         X           Nonsynonymous SNV         dr/17:757947         TP53:NM_000546:exon14:c.C215G;p.P72R         X         X           Nonsynonymous SNV         dr/17:757947         TP53:NM_00034:exon14:c.C135G;p.P72R         X         X           Synonymous SNV         dr/17:757947         TP53:NM_00034:exon14:c.C135G;p.P72R         X         X           Synonymous SNV         dr/17:7579         APC:NM_00034:exon14:c.C19334;p.F1631         X         X           Synonymous SNV         dr/17:7579         APC:NM_00034:exon14:c.C195G;p.P567P         X         X           Synonymous SNV         dr/12:5549063         APC:NM_00036:exon14:c.C116374;p.714931         X         X           Synonymous SNV         dr/12:5539464         RFR:NM_00038:exon14:c.C11632;p.P567P         X         X           Synonymous SNV         dr/12:55549163         RFR:NM_00026:exon14:c.C1516;p.P72R		EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	qΧ	×	qΧ	dX
Synonymals/V         chr11:53424         HRAStNM_005343:exon1:c.C181Cp.H27H         X         X           Nonsynonymous SNV         chr12:5398280         KRAStNM_003346:exon2:c.C33C;p.C12A         X         X           Nonsynonymous SNV         chr17:577120         T533:NM_00546:exon8:c.C63167;p.72H         X         X           Nonsynonymous SNV         chr17:577120         T533:NM_000546:exon8:c.C63167;p.72H         X         X           Nonsynonymous SNV         chr17:577120         T533:NM_000546:exon4:c.C2156;p.72R         X         X           Synonymous SNV         chr5:112175769         APC:NM_00038:exon14:c.C1953A;p.1611         X         X           Synonymous SNV         chr5:112175769         APC:NM_00038:exon14:c.C1953A;p.17493T         X         X           Synonymous SNV         chr5:112175769         APC:NM_000238:exon14:c.C1953A;p.17493T         X         X           Synonymous SNV         chr5:112175769         APC:NM_000238:exon14:c.C1953A;p.17493T         X         X           Synonymous SNV         chr13:35138         RFR:NM_000546:exon4:c.C2156;p.75R         X         X           Nonsynonymous SNV         chr13:35138         RFR:NM_00528:exon10:c.C4479A;p.11493T         X         X           Nonsynonymous SNV         chr13:351386:exon6:c.C33616,p.0786         X         X<		RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	×	×	×
Nonsynonymous SNV         chr12:25398280         KRAS:NM_033360:exon2::CG35C;pC12A         X         X           Nonsynonymous SNV         chr12:25392244         KDR:NM_002533:exon11::.A1141615p.Q472H         X         X           Nonsynonymous SNV         chr17::757120         TP53:NM_000546:exon8::.G818A;p.R273H         X         X*           Nonsynonymous SNV         chr17::7579472         TP53:NM_000546:exon8::.G818A;p.R273H         X         X*           Synonymous SNV         chr17::7579472         TP53:NM_000546:exon8::.G818A;p.R273H         X         X*           Synonymous SNV         chr17::757942         APC:NM_000038:exon14::.C1953A;p.T651T         X         X*           Synonymous SNV         chr4:1807894         FGR3:NM_00038:exon14::.C1953A;p.T651T         X         X*           Synonymous SNV         chr3:11217576         APC:NM_00038:exon14::.C1953A;p.T651T         X         X*           Synonymous SNV         chr3:11217576         APC:NM_00038:exon14::.C1953A;p.T651T         X         X*           Synonymous SNV         chr10::35393464         KT:NM_002905:exon13::.C1317ip.C195G         X         X*           Nonsynonymous SNV         chr17::559424         TP53:NM_000546:exon14::.C13157ip.C105G         X         X*           Nonsynonymous SNV         chr17::559424         TP53:NM_0002		HRAS	Synonym3NV	chr11:534242	HRAS:NM_005343:exon2:c.T81C:p.H27H	×	×	×	×	$\times$
Nonsynonymous SNV         chr12:25398280         KRS:NM_003360:econ2:cG35C;p.G12A         X         X           Nonsynonymous SNV         chr12:557120         TP53:NM_000546:econ11:c.A1416Tp.Q472H         X         X           Nonsynonymous SNV         chr17:557420         TP53:NM_000546:econ11:c.A1416Tp.Q472H         X         X           Nonsynonymous SNV         chr17:55742         TP53:NM_000546:econ4:c.C215G;p.P2R         X         X           Synonymous SNV         chr3:11217556         APC:NM_000142:econ14:c.C1953Ap.T651T         X         X           Synonymous SNV         chr4:1807894         FGR3:NM_000142:econ14:c.C1953Ap.T651T         X         X           Synonymous SNV         chr4:1807894         RFR.NM_00038:econ14:c.C1953Ap.T651T         X         X           Synonymous SNV         chr3:112175769         APC:NM_00038:econ14:c.C1953Ap.T651T         X         X           Synonymous SNV         chr3:112175769         APC:NM_00038:econ13:c.C2361Ap.Q787Q         X         X           Synonymous SNV         chr3:112175769         APC:NM_00036:econ13:c.C2361Ap.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFT.NM_020505:econ10:c.C16954Ap.T1493T         X         X           Nonsynonymous SNV         chr10:43613843         RFT.NM_000225:econ10:c.C16764PG1 <td>Colorectal adenoc</td> <td>arcinoma</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Colorectal adenoc	arcinoma								
Nonsynonymous SNV         dri4:53727120         KDR:NM_000546:exonf1:c.A1416Tp,Q472H         X         X           Nonsynonymous SNV         dri7:577120         TP53:NM_000546:exonf1:c.A1416Tp,Q472H         X         X           Nonsynonymous SNV         dri7:1757742         TP53:NM_000546:exonf3:c.G818Ap,R23H         X         X           Synonymous SNV         dri5:112175576         APC:NM_0000346:exonf3:c.C13657p,Q1429X         X         X           Synonymous SNV         dri4:1807894         FGR3:NM_000142:exon14:c.C1953Ap,T1493T         X         X           Synonymous SNV         dri5:112175769         APC:NM_00038:exon16:c.C44879Ap,T1493T         X         X           Synonymous SNV         dri5:112175769         APC:NM_00038:exon16:c.C4479Ap,T1493T         X         X           Synonymous SNV         dri7:55749063         RFR:NM_000222:exon13:c.C23014p,0769P         X         X           Synonymous SNV         dri7:12175769         APC:NM_0002328:exon13:c.C2361Ap,0769P         X         X           Nonsynonymous SNV         dri7:5579440         RRF:NM_0002328:exon13:c.C2361Ap,0769P         X         X           Nonsynonymous SNV         dri1:557944         RRF:NM_002328:exon13:c.C1361Ap,11691         X         X           Nonsynonymous SNV         dri1:5579410         RRF:NM_002328:exon13:c.C13		KRAS	Nonsynonymous SNV	chr12:25398280	KRAS:NM_033360:exon2:c.G35C:p.G12A	×	×	×	×	×
Nonsynonymous SNV         chr17:757120         TP53:NM_000546:exon8::C618Ap.R273H         X         X*           Nonsynonymous SNV         chr17:7579472         TP53:NM_000546:exon8::C215G:p.P72R         X         X*           Stop codon gain         chr5:11217576         APC:NM_000546:exon14::C1953Ap.1651T         X         X*           Synonymous SNV         chr3:112175769         APC:NM_000038:exon14::C1953Ap.1651T         X         X*           Synonymous SNV         chr3:112175769         APC:NM_000038:exon14::C1953Ap.T651T         X         X*           Synonymous SNV         chr3:112175769         APC:NM_000038:exon14::C1953Ap.T651T         X         X*           Synonymous SNV         chr3:5141050         PDGFRA:NM_005208:exon13::C4704;p17493T         X         X*           Synonymous SNV         chr1:355249063         EGR:NM_00038:exon13::C47704;p17493T         X         X*           Synonymous SNV         chr10:43613843         RET:NM_00038:exon13::C47304;p17691         X         X*           Nonsynonymous SNV         chr10:7559464         KRS:NM_00336(exon2::C3367;p17691         X         X*           Nonsynonymous SNV         chr15:5539464         RT:NM_00205(exon13::CC3167;p.P367F         X         X*           Nonsynonymous SNV         chr17:5539464         RT:NM_002024(exon12::C1953Ap.16		KDR	Nonsynonymous SNV	chr4:55972974	KDR:NM_002253:exon11:c.A1416T;p.Q472H	×	×	×	×	×
Nonsynonymous SNV         chr17;7579472         TF53:NM_000546:exon4:c.C215G;p.P72.R         X         X*           Styp coden gain         chr3:112175576         APC:NM_000038:exon16:c.C4285T;p.Q1429X         X         X*           Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.G1953A;p.1651T         X         X*           Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.G1953A;p.1651T         X         X*           Synonymous SNV         chr4:55141050         PDGFRA:NM_00058:exon12:c.A1701G;p.P567P         X         X*           Synonymous SNV         chr3:112175769         APC:NM_00038:exon13:c.G1953A;p.11493T         X         X*           Synonymous SNV         chr1:3613843         RFI:NM_00528:exon13:c.G2361A;p.Q787Q         X         X*           Nonsynonymous SNV         chr1:35539464         RFI:NM_020252:8:xon13:c.G2361A;p.Q787Q         X         X*           Nonsynonymous SNV         chr1:2:55393464         K1F:NM_02022:exon13:c.G2361A;p.G787Q         X         X*           Nonsynonymous SNV         chr1:2:55393464         K1F:NM_000222:exon13:c.G165G;p.P75R         X         X*           Nonsynonymous SNV         chr1:2:55393464         K1F:NM_00222:exon10:c.G165G;p.P75R         X         X*           Nonsynonymous SNV         chr1:2:5539464 <td< td=""><td></td><td>TP53</td><td>Nonsynonymous SNV</td><td>chr17:7577120</td><td>TP53:NM_000546:exon8:c.G818A:p.R273H</td><td>×</td><td>чX</td><td>×</td><td>×</td><td><math>\times</math></td></td<>		TP53	Nonsynonymous SNV	chr17:7577120	TP53:NM_000546:exon8:c.G818A:p.R273H	×	чX	×	×	$\times$
Stop codon gain         chr5:112175576         APC:NM_000038:exon16:c.C4285Tp.Q1429X         X         X           Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.C1953A;p.T651T         X         X*           Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:c.A1701G;p.P567P         X         X*           Synonymous SNV         chr5:112175769         APC:NM_000038:exon16:c.C4493A;p.T1493T         X         X*           Synonymous SNV         chr5:112175799         APC:NM_000038:exon16:c.C4479A;p.T1493T         X         X*           Synonymous SNV         chr10:43613843         RFI:NM_000238:exon16:c.C4364p.C179T         X         X*           Nonsynonymous SNV         chr12:2539280         KRAS:NM_00038:exon16:c.C4364p.C120         X         X*           Nonsynonymous SNV         chr12:25393464         KTI:NM_000296:exon13:c.C2361A;p.Q167         X         X           Nonsynonymous SNV         chr12:5593464         KTI:NM_000296:exon13:c.C354p.C12D         X         X           Nonsynonymous SNV         chr12:5593464         KTI:NM_000296:exon14:c.C1365p.P72R         X         X           Nonsynonymous SNV         chr13:5593464         KTI:NM_002896:exon14:c.C1365p.P72R         X         X           Synonymous SNV         chr13:5579412         DPGFRA:NM_006206:e		TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×	чX	×	×	dX
Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14::C1953Ap.T651T         X         Velocity           Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12::CA1701Cip.P567P         X         X           Synonymous SNV         chr5:112175769         APC:NM_00038:exon16::C4479A;p.T1493T         X         X           Synonymous SNV         chr5:112175769         APC:NM_00038:exon16::C4479A;p.T1493T         X         X           Synonymous SNV         chr7:55249063         EGFR:NM_00528:exon13::C.C3307Fp.L769L         X         X           Nonsynonymous SNV         chr1:3539280         KRAS:NM_0033360:exon13::C.C3367;p.G12D         X         X           Nonsynonymous SNV         chr1:2:5398280         KRAS:NM_000222:exon13::C.C3367;p.G12D         X         X           Nonsynonymous SNV         chr1:5759442         TF53:NM_000222:exon13::C.C3367;p.G12D         X         X           Nonsynonymous SNV         chr1:5759443         K1FNM_000222:exon13::C.C31610;f.G16         X         X           Synonymous SNV         chr2:5593464         K1FNM_000222:exon14::C.G1653A;p.G12D         X         X           Synonymous SNV         chr1:7757942         TF53:NM_000142:exon14::C.G1653A;p.G12D         X         X           Synonymous SNV         chr1:5754905         PCFRA:NM_005208:exon		APC	Stop codon gain	chr5:112175576	APC:NM_000038:exon16:c.C4285T:p.Q1429X	×	×	×	×	$\times$
Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:c.A1701G;p.F567P         X         X           Synonymous SNV         chr5:112175769         APC:NM_00038:exon16:c.G479A;p.T1493T         X         X           Synonymous SNV         chr7:55249063         EGFR:NM_00038:exon16:c.G479A;p.T1493T         X         X           Synonymous SNV         chr7:55249063         EGFR:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           Nonsynonymous SNV         chr10:43613843         RFT:NM_002975:exon13:c.G2307T;p.L769L         X         X           Nonsynonymous SNV         chr12:25393464         KTF:NM_00022:exon10:c.G1621Cp.M541L         X         X           Nonsynonymous SNV         chr17:757942         TP53:NM_000546:exon4:c.C315T;p.L769L         X         X           Synonymous SNV         chr17:757942         TP53:NM_000546:exon4:c.C151G;p.P72R         X         X           Synonymous SNV         chr17:757942         TP63:NM_000546:exon4:c.C191G;p.P567P         X         X           Synonymous SNV         chr4:1807894         FGFR3:NM_00528:exon12:c.A1701G;p.P567P         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_00528:exon13:c.G1953A;p.1651T         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_00528:exon13:c.G1		FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	٩X	×	×	×
Synonymous SNV         chr5:112175769         APC:NM_00038:exon16:c.G44794;p.T1493T         X         X           Synonymous SNV         chr7:55249063         EGFR:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr1:55249063         EGFR:NM_005228:exon16:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFT:NM_020975:exon13:c.G2307T;p.L769L         X         X           Nonsynonymous SNV         chr12:5593464         KTF:NM_000222:exon10:c.G35A;p.G12D         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000232:exon10:c.G15G;p.P75R         X         X           Synonymous SNV         chr17:7579472         IDH1:NM_005896:exon4:c.C215G;p.P75R         X         X           Synonymous SNV         chr17:7579472         IDH1:NM_005896:exon14:c.C115G;p.P75R         X         X           Synonymous SNV         chr17:7579472         IDH1:NM_005896:exon14:c.C115G;p.P75R         X         X           Synonymous SNV         chr4:1807894         FGFR3:NM_00142:exon14:c.C1953A;p.G105G         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_005208:exon13:c.C2361A;p.Q787Q         X         X           Synonymous SNV         chr4:551341050         PDGFRA:NM_005228:exon13:c.C193		PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×	$\times$
Synonymous SNV         chr7:55249063         EGFR:NM_00528:exon20::C2361A;p.Q787Q         X           Synonymous SNV         chr10:43613843         RET:NM_020975:exon13::C2307T;p.L769L         X         X           Nonsynonymous SNV         chr10:43613843         RET:NM_020975:exon13::C2307T;p.L769L         X         X           Nonsynonymous SNV         chr12:25398280         KRAS:NM_03360:exon2::C336A;p.G12D         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000222:exon10::C.1621C;p.M541L         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000246:exon4::C.215G;p.P72R         X         X           Synonymous SNV         chr13:0209113192         IDH1:NM_005896:exon4::C.215G;p.P72R         X         X           Synonymous SNV         chr3:55249063         PGFR3:NM_000142:exon14::C.G1953A;p.I651T         X         X           Synonymous SNV         chr3:55249063         PGFR3:NM_000142:exon14::C.G1953A;p.I651T         X         X           Synonymous SNV         chr3:55249063         PGFR3:NM_000528:exon13::C.G2361A;p.Q787Q         X         X           Synonymous SNV         chr3:51343         RFI:NM_00528:exon13::C.G1953A;p.I651T         X         X           Synonymous SNV         chr3:51341050         PGFR3:NM_00528:exon13::C.G2361A;p.Q787Q<		APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×	×	×	×	×
Synonymous SNV         Chr10:43613843         RET:NM_020975:exon13:C.C2307T;p.L769L         X         X           Nonsynonymous SNV         chr12:25398280         KRAS:NM_033360:exon2:C.G35A;p.G12D         X         X           Nonsynonymous SNV         chr17:757942         TP53:NM_000222:exon10:C.A1621C;p.M541L         X         X           Nonsynonymous SNV         chr17:757942         TP53:NM_000546:exon4:C.C215G;p.P72R         X         X           Synonymous SNV         chr17:757942         TP53:NM_000546:exon4:C.C215G;p.P72R         X         X           Synonymous SNV         chr4:1807894         FGFR3:NM_000546:exon4:C.C215G;p.P72R         X         X           Synonymous SNV         chr4:55141050         DDGFRA:NM_005896:exon4:C.C315T;p.G105G         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_005298:exon13:C.C41761G;p.P567P         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_00528:exon13:C.G2361A;p.Q787Q         X         X           Synonymous SNV         chr15:55249063         RFI:NM_020975:exon13:C.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFI:NM_020975:exon13:C.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFI:NM_020975:exon13:C.G2		EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	чX	×	×	dX
Nonsynonymous SNV         chr12:25398280         KRAS:NM_03360:exon2:c.G35A;p.G12D         X           Nonsynonymous SNV         chr4:55593464         k11;NM_000222:exon10:c.A1621C;p.M541L         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000546:exon10:c.A1621C;p.M541L         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000546:exon10:c.A1621C;p.M541L         X         X           Synonymous SNV         chr17:5579472         TP53:NM_000546:exon10:c.A1621C;p.M541L         X         X           Synonymous SNV         chr2:209113192         IDH1:NM_005896:exon4:c.C215G;p.P72R         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_005986:exon4:c.C315T;p.G105G         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_00528:exon14:c.G1953A;p.T651T         X         X           Synonymous SNV         chr4:55141050         PDGFRA:NM_00528:exon13:c.G1953A;p.T651T         X         X           Synonymous SNV         chr1:55249063         EGFR:NM_00528:exon13:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RET:NM_020975:exon13:c.G2307T;p.L769L         X         X           Synonymous SNV         chr10:43613843         RAT:NM_020975:exon13:c.G2307T;p.L769		RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	×	×	$\times$
Nonsynonymous SNV         chr12:25398280         KRAS:NM_03360:exon2:c.G35A;p.G12D         X         X           Nonsynonymous SNV         chr4:55593464         KIT:NM_000222:exon10:c.A1621C;p.M541L         X         X           Nonsynonymous SNV         chr17:7579472         TP53:NM_000546:exon4:c.C215G;p.P72R         X         X           Synonymous SNV         chr17:7579472         TP53:NM_000546:exon4:c.C215G;p.P72R         X         X           A         Synonymous SNV         chr2:209113192         IDH1:NM_005896:exon4:c.C315T;p.G105G         X         X           A         Synonymous SNV         chr4:1807894         FGFR3:NM_005896:exon4:c.C315T;p.G105G         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_005206:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_005205:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_005205:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr1:55249063         RT:NM_005228:exon14:c.G1953A;p.T691L         X         X           Synonymous SNV         chr10:43613843         RT:NM_005228:exon14:c.G1953A;p.PG81         X         X <td>Low-grade ovariar</td> <td>serous carcinoma</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Low-grade ovariar	serous carcinoma								
Nonsynonymous SNV         chr4:55593464         KIT:NM_000222:exon10:c.A1621C;p.M5411         X         X           Nonsynonymous SNV         chr17:579472         TP53:NM_000246:exon4:c.C215G;p.P72R         X         X           Synonymous SNV         chr17:579472         TP53:NM_000546:exon4:c.C215G;p.P2R         X         X           A         Synonymous SNV         chr2:209113192         IDH1:NM_005896:exon4:c.C315T;p.G105G         X         X           A         Synonymous SNV         chr4:1807894         FGR3:NM_000142:exon14:c.G1953A;p.G105G         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_000142:exon14:c.G1953A;p.G105P567P         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           A         Synonymous SNV         chr10:43613843         RET:NM_020975:exon13:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFT:NM_020975:exon13:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon20:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon13:c.G2307T;p.L769L         X         X		KRAS	Nonsynonymous SNV	chr12:25398280	KRAS:NM_033360:exon2:c.G35A:p.G12D	×	×	×	×	$\times$
Nonsynonymous SNV         chr17:7579472         TP53:NM_000546:exon4:c.C215G:p.P72R         X         X           Synonymous SNV         chr2:209113192         IDH1:NM_005896:exon4:c.C315T:p.G105G         X         X           A         Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:c.A1701G;p.P567P         X         X           Synonymous SNV         chr10:43613843         FGFR:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFT:NM_020975:exon13:c.G2307Fp.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon2:c.T81C;p.H27H         X         X		KIT	Nonsynonymous SNV	chr4:55593464	KIT:NM_000222:exon10:c.A1621C:p.M541L	×	×	×	×	×
Synonymous SNV         chr2:209113192         IDH1:NM_005896:exon4:c.C315T;p.G105G         X         X           A         Synonymous SNV         chr4:1807894         FGFR3:NM_00142:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:c.A1701G;p.P567P         X         X           A         Synonymous SNV         chr15:5249063         EGFR:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RET:NM_020975:exon13:c.G2307T;p.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon20:c.G181C;p.H27H         X         X		TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×	×	×	×	$\times$
Synonymous SNV         chr4:1807894         FGFR3:NM_000142:exon14:c.G1953A;p.T651T         X         X           A         Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:c.A1701G;p.P567P         X         X           Synonymous SNV         chr1:55249063         EGFR:NM_005228:exon20:c.G2361A;p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RFI:NM_020975:exon13:c.G23071;p.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon20:c.G23071;p.L769L         X         X		IDH1	Synonymous SNV	chr2:209113192	IDH1:NM_005896:exon4:c.C315T;p.G105G	×	×	×	×	×
RA         Synonymous SNV         chr4:55141050         PDGFRA:NM_006206:exon12:C.A1701G:p.P567P         X         X           Synonymous SNV         chr7:55249063         EGFR:NM_005228:exon20:C.G2361A:p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RET:NM_005228:exon13:C.G2361A:p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RET:NM_005238:exon13:C.G23071;p.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon2:C.T81C:p.H27H         X         X		FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	×	×	×	$\times$
Synonymous SNV         chr7:55249063         EGFR:NM_005228:exon20:c.G2361A:p.Q787Q         X         X           Synonymous SNV         chr10:43613843         RET:NM_020975:exon13:c.G2307T;p.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon20:c.T81C;p.H27H         X         X		PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×	×
Synonymous SNV         chr10:43613843         RET:NM_020975:exon13:c.G2307T;p.L769L         X         X           Synonymous SNV         chr11:534242         HRAS:NM_005343:exon2:c.T81C;p.H27H         X         X		EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	×	×	×	$\times$
Synonymous SNV chr11:534242 HRAS:NM_005343:exon2:c.T81C:p.H27H X X		RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	×	×	×
		HRAS	Synonymous SNV	chr11:534242	HRAS:NM_005343:exon2:c.T81C:p.H27H	×	×	×	×	$\times$

	Gene	Variant type	Genomic	Variant	_	Laboratory ID <sup>a</sup>	ory ID	
tuffiour			coordinates		1 2	2 3	3 4	_
High-grade ovaria	High-grade ovarian serous carcinoma							
	TP53	Stop codon gain	chr17:7577046	TP53:NM_000546:exon8:c.G892T;p.E298X	×	×	×	
	KIT	Nonsynonymous SNV	chr4:55593464	KIT:NM_000222:exon10:c.A1621C:p.M541L	×	×	××	
	MET	Nonsynonymous SNV	chr7:116411990	MET:NM_001127500:exon14:c.C3029T;p.T10101	×	×	××	
	TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×			
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×			
	PDCFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P				
	PDCFRA	Synonymous SNV	chr4:55152040	PDGFRA:NM_006206:exon18:c.C2472T;p.V824V		××	×	
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T				
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×		dX >	q
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L				
	RET	Synonymous SNV	chr10:43615633	RET:NM_020975:exon15:c.C2712G:p.S904S	×			
	HRAS	Synonymous SNV	chr11:534242	HRAS:NM_005343:exon2:c.T81C:p.H27H			×	
Liver adenocarcinoma	oma							
	IHUI	Nonsynonymous SNV	chr2:209113113	IDH1:NM_005896:exon4:c.C394T;p.R132C	×	××	×	
	APC	Nonsynonymous SNV	chr5:112175240	APC:NM_000038:exon16:c.G3949C:p.E1317Q				q
	TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×		××	
	1DH1	Synonymous SNV	chr2:209113192	IDH1:NM_005896:exon4:c.C315T;p.G105G	×			
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T				
	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P		×	×	
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×			
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	×	dX Xb	b X <sup>b</sup>
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L			×	
Parathyroid carcinoma	oma							
	PIK3CA	Nonsynonymous SNV	chr3:178927410	PIK3CA:NM_006218:exon7:c.A1173G:p.I391M	×	×	×	
	ATM	Nonsynonymous SNV	chr11:108138003	ATM:NM_000051:exon17:c.T2572C:p.F858L	×	×	×	
	TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×		××	
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T				
	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	
	PDGFRA	Synonymous SNV	chr4:55152040	PDGFRA:NM_006206:exon18:c.C2472T;p.V824V		×		
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×			
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×			
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	××	

Specimen	Gene	Variant type	Genomic coordinates	Variant		Labor	Laboratory ID <sup>a</sup>	Da	
					-	2	3	4	5
<sup>7</sup> Lung adenocarcinoma	oma								
	ERBB2	In-frame insertion	chr17:37880981	ERBB2:NM_004448:exon20:c.2310_2311ins GCATACGTGATG: p.E770delinsEAYVM	×	×	×	$\times$	$\times$
	TP53	Nonsynonymous SNV	chr17:7577509	TP53:NM_000546:exon7:c.G772A:p.E258K	чX	×	×	×	×
	KIT	Nonsynonymous SNV	chr4:55593464	KIT:NM_000222:exon10:c.A1621C:p.M541L	×	$\times$	$\times$	×	$\times$
	KDR	Nonsynonymous SNV	chr4:55972974	KDR:NM_002253:exon11:c.A1416T;p.Q472H	×	×	×	×	×
	TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×	$\times$	×	$\times$	$\times$
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	dX	$\times$	$\times$	$\times$
	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	$\times$	×	$\times$	$\times$
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A;p.T1493T	×	×	×	×	×
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	×	×	×	$^{\rm q}\times$
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	×	×	$\times$
8 High-grade ovarian serous carcinoma	n serous carcinoma								
	TP53	Non-frameshift deletion	chr17:7577518	TP53:NM_000546:exon7:c.754_756del:p.252_252del	×	×	×	×	$\times$
	TP53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	ЧX	×	×	×	×
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	×	×	×	$\times$
	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×	×
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×	$\times$	$\times$	$\times$	$\times$
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	dX <sup>b</sup>	×	×	×	×
	NOTCH1	Synonymous SNV	chr9:139397767	NOTCH1:NM_017617:exon27:c.G5034T;p.L1678L	чX	×	×	×	$\times$
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307Tip.L769L					
	RET	Synonymous SNV	chr10:43615633	RET:NM_020975:exon15:c.C2712G:p.S904S	×	×	×	×	$\times$
	HRAS	Synonymous SNV	chr11:534242	HRAS:NM_005343:exon2:c.T81C:p.H27H	×	×	×	×	$\times$
9 High-grade ovarian serous carcinoma	n serous carcinoma								
	TP53	Nonsynonymous SNV	chr13:28610183	TP53:NM_000546:exon6:c.A659G:p.Y220C	×	$\times$	×	$\times$	$\times$
	THA	Nonsynonymous SNV	chr3:10188296	VHL:NM_000551:exon2:c.A439G:p.I147V	×	×	×	×	×
	MET	Nonsynonymous SNV	chr7:116340262	MET:NM_001127500:exon2:c.A1124G:p.N375S	×	$\times$	×	$\times$	$\times$
	TP53	Nonsynonymous SNV	chr17:7578190	TP53:NM_000546:exon4:c.C215G:p.P72R	×	×	×	×	×
	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	$\times$	×	$\times$	$\times$
	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×	×
	APC	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×	$\times$	$\times$	$\times$	$\times$
	EGFR	Synonymous SNV	chr7:55249063	EGFR:NM_005228:exon20:c.G2361A:p.Q787Q	×	×	×	×	×
	MET	Synonymous SNV	chr7:116339672	MET:NM_001127500:exon2:c.C534T;p.S178S	×	$\times$	$\times$	$\times$	$\times$
	RET	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G23077ip.L769L	×	×	×	×	$\times$

TABLE II Continued

Specimen	Gene	אמוומווו ואףכ	coordinates				Laburatury IL	
minour			coordinates		-	5	4	IJ
10 Lung squamous cell carcinoma	carcinoma							
TP53	53	Nonsynonymous SNV	chr17:7577120	TP53:NM_000546:exon8:c.G818T;p.R273L	чX	×	×	×
KIT		Nonsynonymous SNV	chr4:55593464	KIT:NM_000222:exon10:c.A1621C:p.M541L	×	×	×	×
TP53	53	Nonsynonymous SNV	chr17:7579472	TP53:NM_000546:exon4:c.C215G:p.P72R	×	×	×	×
FG	FGFR3	Synonymous SNV	chr4:1807894	FGFR3:NM_000142:exon14:c.G1953A:p.T651T	×	×	X	×
PD	PDGFRA	Synonymous SNV	chr4:55141050	PDGFRA:NM_006206:exon12:c.A1701G:p.P567P	×	×	×	×
APC	U.	Synonymous SNV	chr5:112175769	APC:NM_000038:exon16:c.G4479A:p.T1493T	×	×	×	×
RET	L	Synonymous SNV	chr10:43613843	RET:NM_020975:exon13:c.G2307T;p.L769L	×	×	×	×

4 were ovarian tumours, a site from which large surgical specimens with sufficient cellularity and lack of significant necrosis were more readily available. Only 2 lung cancer samples and 1 colorectal cancer sample were included because of the typically small tumour specimens obtained for those tumour types, although lung and colorectal cancers represent the tumours that most commonly undergo NGS testing as the standard of care in Ontario. That bias in sample selection is likely to have affected the interpretation or reporting aspects of this PT, because all participating laboratories routinely test lung and colorectal cancers, but only 3 of the 5 participating laboratories typically report on ovarian cancer.

Another issue related to the use of FFPE tumour tissue is potential tumour heterogeneity, which can contribute to variability in the detection of variants. A recent survey involving 111 laboratories assessed inter-laboratory technical performance for NGS-based solid tumour oncology assays and identified substantial agreement (>98%) in the accuracy of detection for single nucleotide variants occurring at a VAF more than 15%<sup>2</sup>. Indeed, although we observed no difference in the final exonic variants identified in the present study (98 of 98), variability in the VAF and depth of coverage was evident during quality assessment of the vcF file data. Although that variability might be attributable to tumoural heterogeneity, it might also result from differences in pre-analytic sample processing or NGS quality or in differences in the sequencing technology, and further delineating the causes of those differences in VAF and coverage depth is not possible. It is also noteworthy that, although complete concordance was observed in the technical identification of the 98 variants, 28 of 98 variants were identified by 1 or more sites below the lower VAF and quality threshold cut-offs defined in the study.

With respect to the interpretation and reporting of variants in tumour molecular profiling, discrepancies were observed: only 3 variants were selected as clinically reportable by all participating sites, and only 10 variants were concordantly reported by 3 or more sites. In part, those results reflected site-specific interpretation of the instructions for the PT scheme (supplemental Table 1), because some laboratories reported only variants in genes routinely reported in clinical practice at that institution (rather than those reported in the OCTANE study), regardless of tumour type. This site-specific reporting practice highlights the significant gap in the classification of what is considered a "clinically reportable" variant in the Ontario context and likely reflects practice in other Canadian provinces, because national standards for somatic variant interpretation do not currently exist. With respect to using published classification schemes to classify variants as "actionable," there was also no consensus concerning the classification scheme applied, with 3 sites applying the AMP/ASCO/CAP guideline<sup>6</sup>, 1 using the Sukhai *et al.* guideline<sup>7</sup>, and 1 not using a guideline. Of the sites that used the AMP/ASCO/CAP guideline, 2 included only tier I or II variants as "clinically reportable"; another laboratory included tier I-IV variants. That observation underscores issues related to the understanding of the PT instructions, because tier III and IV variants are generally not considered clinically actionable or reportable.

Variant was identified at below laboratory-defined thresholds

0

Specimen	Gene	Transcript	HGVS	VS		Variant	Variant reported by site	' site		0	oncordan	Concordantly reported variants	ed variants	
tumour		I	cDNA	Protein	Site 1	Site 2	Site 3	Site 4	Site 5	All sites	≥4 Sites	≥3 Sites	≥2 Sites	1 Site
1 Melanoma														
	KDR	NM_002253.2	c.1416A>T	p.Gln472His		X Tr. III/Cl. 3								×
	KIT	NM_000222.2	c.1621A>C	p.Met541Leu		X Tr. IV/Cl. 4								×
	NRAS	NM_002524.4	c.181C>A	p.Gln61Lys	X Tr. I/Cl. 1	X X Tr. I/Cl. 1 Tr. II/Cl. 2	X Tr. I/II	×Û	X Tr. I/Cl. 1	×				
	TP53	NM_000546.5	c.380C>T	p.Ser127Phe		X Tr. II/Cl. 2			X Tr. III/Cl. 3				×	
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
2 Colorectal adenocarcinoma	tdenocar	cinoma												
	APC	NM_000038.5	c.4285C>T	p.Gln1429Ter		X Tr. II/Cl. 2			X Tr. 11/Cl. 2				×	
	KDR	NM_002253.2	c.1416A>T	p.Gln472His		X Tr. III/Cl. 3								×
	KRAS	NM_03360.3	c.35G>C	p.Gly12Ala	X Tr. I/Cl. 1	X X Tr. I/Cl. 1 Tr. I/Cl. 1	X Tr. I/II	×Û	X X (NC) Tr. I/Cl. 1	×				
	TP53	NM_000546.5	c.818G>A	p.Arg273His		X Tr. II/Cl. 2			X Tr. II/Cl. 2				×	
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
3 Low grade c	ovarian su	Low grade ovarian serous carcinoma												
	KIT	NM_000222.2	c.1621A>C	p.Met541Leu		X Tr. IV/Cl. 4								×
	KRAS	NM_033360.2	c.35G>A	p.Gly12Asp	X Tr. II/Cl. 2	X X Tr. II/Cl. 2 Tr. II/Cl. 2	X Tr. I/II	×Û	X X (NC) Tr. II/Cl. 2	×				
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
4 High grade	ovarian s	High grade ovarian serous carcinoma												
	KIT	NM_000222.2	c.1621A>C	p.Met541Leu		X Tr. IV/Cl. 4								×
	MET	NM_001127500.2	c.3029C>T	p.Thr1010lle	·	X Tr. III/Cl. 3								×

Specimen	Gene	Transcript	HGVS	SV		Variant	Variant reported by site	site		Ū	Concordan	Concordantly reported variants	d variants	
tumour			cDNA	Protein	Site 1	Site 2	Site 3	Site 4	Site 5	All sites	≥4 Sites	≥3 Sites	≥2 Sites	1 Site
4 High grade	e ovarian se	High grade ovarian serous carcinoma continued	ntinued											
	TP53	NM_000546.5	c.892G>T	p.Glu298Ter	X Tr. 111/Cl. 3	X X Tr. III/Cl. 3 Tr. II/Cl. 2			X Tr. II/Cl. 2			×		
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
5 Liver aden	Liver adenocarcinoma													
	APC	NM_000038.5	c.3949G>C	p.Glu1317Gln		X Tr. II/Cl. 2								×
	1H11	NM_005896.2	c.394C>T	p.Arg132Cys	X Tr. I/Cl. 1	Tr. I/Cl. 1 Tr. II/Cl. 2 Tr. I/II	Tr. I/II	·	X Tr. II/Cl. 2		×			
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
6 Parathyroic	Parathyroid carcinoma													
	ATM	NM_000051.3	c.2572T>C	p.Phe858Leu		X Tr. III/Cl. 3								×
	PIK3CA	NM_006218.3	c.1173A>G	p.Ile391Met		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
7 Lung aden	Lung adenocarcinoma													
	ERBB2	NM_004448.2	c.2313_2324 dupATACGT GATGGC	p.Tyr775_ Ala778 dup	X Tr. III/Cl. 3	X X X Tr. III/CL 3 Tr. II/CL 2 Tr. II/CL 2	X Fr. 11/Cl. 2	·	X Tr. II/Cl. 2		×			
	KDR	NM_002253.2	c.1416A>T	p.Gln472His		X Tr. III/Cl. 3								×
	KIT	NM_000222.2	c.1621A>C	p.Met541Leu		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.772G>A	p.Glu258Lys	X Tr. III/Cl. 3	X X Tr. III/Cl. 3 Tr. II/Cl. 2		·	X Tr. 11/Cl. 2			×		
8 High grade	e ovarian se	High grade ovarian serous carcinoma												
	NOTCH1	NOTCH1 NM_017617.4	c.5034G>T	p.Leu1678=					Tr III/CL 3					×

Specimen	n Gene	Transcript	H	HGVS		Variant	Variant reported by site	/ site			Concordan	Concordantly reported variants	d variants	
tumour			cDNA	Protein	Site 1	Site 2	Site 3	Site 4	Site 5	All sites	≥4 Sites	≥3 Sites	≥2 Sites	1 Site
8 High gra	ıde ovarian	High grade ovarian serous carcinoma continued	ntinued											
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
9 High gra	ıde ovarian	High grade ovarian serous carcinoma												
	MET	MET NM_001127500.1 c.1124A>G	c.1124A>G	p.Asn375Ser		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.659A>G	p.Tyr220Cys	X Tr. II/Cl. 2	X X Tr. II/Cl. 2 Tr. II/Cl. 2		-	X Tr. II/Cl. 2			×		
	ΛΗΛ	NM_000551.3	c.439A>G	p.lle147Val		X Tr. III/Cl. 3		F	X Tr. III/Cl. 3				×	
10 Lung si	quamous ce	10 Lung squamous cell carcinoma												
	KIT	NM_000222.2	c.1621A>C	p.Met541Leu		X Tr. IV/Cl. 4								×
	TP53	NM_000546.5	c.818G>T	p.Arg273Leu	X Tr. III/Cl. 3	X X Tr. III/Cl. 3 Tr. II/Cl. 2			X Tr. II/Cl. 2			×		
	TP53	NM_000546.5	c.215C>G	p.Pro72Arg		X Tr. IV/Cl. 4								×
HGVS = HL	iman Genor	HGVS = Human Genome Variation Society; cDNA = complementary DNA; X = variant reported; Tr = tier; Cl = class; NC = variant not classified, but clinically reported.	cDNA = compler	mentary DNA; X = V	variant report	ed; Tr = tier; (	Cl = class; h	4C = varian	t not classifi	ed, but clin	ically repo	orted.		

### CONCLUSIONS

Our pilot molecular profiling PT scheme for solid tumours at 5 clinical laboratories in Ontario demonstrates the value of an analyte-based end-to-end PT approach, and also highlights issues related to selection of sample source material, evaluation of NGS quality, and discrepancies in somatic variant interpretation and reporting. Although complete concordance in the technical identification of variants was observed across laboratories and sequencing platforms, significant variability was found in the definition of those variants considered to be "clinically reportable," compounded by site-specific practices for reporting and variant classification practices. Our pilot study demonstrates a successful PT scheme within the Canadian clinical laboratory context and also demonstrates a need to define the clinically relevant genes and variants to be reported and an appropriate variant classification scheme in solid tumour molecular profiling to reduce cross-institutional inconsistencies.

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#### CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare the following interests: HC reports grants from the Ontario Institute for Cancer Research during the conduct of the study. HF reports nonfinancial support from Thermo Fisher outside the submitted work. BL reports personal fees from Novartis, Bayer, Roche, and AstraZeneca outside the submitted work. BS reports fees from the Ontario Institute for Cancer Research during the conduct of the study. LLS reports other consideration from Merck (compensated), Pfizer (compensated), Celgene (compensated), AstraZeneca/ Medimmune (compensated), MorphoSys (compensated), Roche (compensated), Geneseeq Technology (compensated), Loxo Oncology (compensated), Oncorus (compensated), Symphogen (compensated), Seattle Genetics (compensated); grants from Novartis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, GlaxoSmithKline, Roche/Genentech, Karyopharm, AstraZeneca/Medimmune, Merck, Celgene, Astellas, Bayer, AbbVie, Amgen, Symphogen, Intensity Therapeutics, Mirati Therapeutics, and Shattuck Labs; and other consideration from Agios Pharmaceuticals (spouse) outside the submitted work. PLB is a member of the steering committee for the American Association for Cancer Research Project GENIE, past chair of the Canadian Cancer Trials

Group Investigational New Drug Committee, a member of the executive board for the Breast International Group, a section editor for *The Oncologist* and for *JNCI Cancer Spectrum* outside the submitted work. The remaining authors have no conflicts of interest to disclose.

### **AUTHOR AFFILIATIONS**

\*Toronto, ON: Advanced Molecular Diagnostics Laboratory, Princess Margaret Cancer Centre, University Health Network (Spence, Stockley); Bioinformatics and HPC Core, Princess Margaret Cancer Centre, University Health Network (Stickle); Cancer Genomics Program, Princess Margaret Cancer Centre, University Health Network (Yu, Chow, Siu); Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network (Siu, Bedard); Department of Medicine, University of Toronto (Siu, Bedard); Department of Clinical Laboratory Genetics, University Health Network (Stockley); Department of Laboratory Medicine and Pathobiology, University of Toronto (Stockley); <sup>†</sup>Kingston, ON: Molecular Diagnostics, Kingston Health Sciences Centre (Feilotter); Department of Pathology and Molecular Medicine, Queen's University (Feilotter); <sup>‡</sup>Ottawa, ON: Molecular Oncology Diagnostics Laboratory, The Ottawa Hospital (Lo); Department of Pathology and Laboratory Medicine, University of Ottawa (Lo); §Hamilton, ON: Hamilton Health Sciences and St. Joseph's Healthcare (McCready); Department of Pathology and Molecular Medicine, McMaster University (McCready); London, ON: Pathology and Laboratory Medicine Program, London Health Sciences Centre (Sadikovic); Department of Pathology and Laboratory Medicine, Western University (Sadikovic).

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### APPENDIX A: GENE LISTS FOR MOLECULAR PROFILING ASSAYS

ABL1	EGFR	GNAS	KRAS	PTPN11
AKT1	ERBB2	GNAQ	MET	RB1
ALK	ERBB4	HNF1A	MLH1	RET
APC	EZH2	HRAS	MPL	SMAD4
ATM	FBXW7	IDH1	NOTCH1	SMARCB1
BRAF	FGFR1	JAK2	NPM1	SMO
CDH1	FGFR2	JAK3	NRAS	SRC
CDKN2A	FGFR3	IDH2	PDGFRA	STK11
CSF1R	FLT3	KDR	РІКЗСА	TP53
CTNNB1	GNA11	KIT	PTEN	VHL

 $\label{eq:table_table} \textbf{TABLE AI} \quad \text{Gene list for the amplicon-based Ion AmpliSeq Cancer Hotspot Panel $v2^a$}$ 

<sup>a</sup> Thermo Fisher, Waltham, MA, U.S.A. (includes regions of 50 genes; was used by the 4 participating Ontario laboratories: Juravinski Cancer Centre, Hamilton; London Health Sciences Centre, London; The Ottawa Hospital, Ottawa; and Kingston Health Sciences Centre, Kingston).

TABLE AII Ge	ene list for the SureSelect <sup>a</sup> custom	hybridization captur	e panel of 555 cancer-relate	d genes ("UHN Hi5 Panel")
--------------	---	----------------------	------------------------------	---------------------------

		/	• •	0	· · · · · · · · · · · · · · · · · · ·	
ABL1	CDH2	EWSR1	ІКВКВ	MPL	PMS2	SS18L1
ABL2	CDH20	EXT1	IKBKE	MRE11A	POT1	SSX1
ACTG1	CDH23	EXT2	IKZF1	MSH2	POU5F1	SSX2
ACVR2A	CDH5	EZH2	IL2	MSH6	PPARG	SSX4
ADAMTS20	CDK12	EZR	IL21R	MTOR	PPP2R1A	STAG2
AFF1	CDK4	FAM175A	IL3	MTR	PPP6C	STAT3
AFF3	CDK6	FAM46C	IL6ST	MTRR	PRCC	STAT4
AKAP9	CDK8	FAM5C	IL7R	MUC1	PRDM1	STK11
AKT1	CDKN1B	FANCA	ING4	MUTYH	PRDM16	STK36
AKT2	CDKN2A	FANCC	INHBA	МҮВ	PREX2	SUFU
AKT3	CDKN2B	FANCD2	INPP4B	МҮС	PRKAR1A	SUZ12
ALK	CDKN2C	FANCE	IRF4	MYCL	PRKDC	SYK
AMER1	CEBPA	FANCF	IRF8	MYCN	PSIP1	SYNE1
ANKRD24	CHEK1	FANCG	IRS2	MYD88	PTCH1	SYT1
APC	CHEK2	FANCL	ITGA10	MYH11	PTEN	TAF1
AR	CHIC2	FAS	ITGA9	MYH9	PTGS2	TAF1L
ARAF	CIC	FBXW7	ITGB2	NBN	PTPN11	TAL1
ARFGAP3	CKS1B	FGF10	ITGB3	NCOA1	PTPRD	TBX22
ARFRP1	СМРК1	FGF14	JAK1	NCOA2	PTPRT	TCF12
ARID1A	COL1A1	FGF19	JAK2	NCOA4	RAC1	TCF3
ARID2	CRBN	FGF23	JAK3	NCOR2	RAD21	TCF7L1
ARNT	CREB1	FGF3	JUN	NF1	RAD50	TCF7L2
ASPSCR1	CREB3L2	FGF4	KAT6A	NF2	RAD51	TCL1A
ASXL1	CREBBP	FGF6	KAT6B	NFE2L2	RAD51C	TERT
ATF1	CRKL	FGFR1	KDM5A	NFKB1	RAD51D	TET1
ATM	CRLF2	FGFR2	KDM5C	NFKB2	RAF1	TET2
ATR	CRTC1	FGFR3	KDM6A	NFKBIA	RALGDS	TFE3

ATRX	CSF1R	FGFR4	KDR	NIN	RARA	TGFB1
AURKA	CSF3R	FH	KEAP1	NKX2–1	RB1	TGFBR2
AURKB	CSMD3	FIP1L1	KIT	NLRP1	RBM15	TGM7
AURKC	CSNK2B	FLCN	KLF6	NOTCH1	RECQL4	THBS1
AXL	CTCF	FLI1	KLHL6	NOTCH2	REL	TIMP3
B2M	CTDNEP1	FLT 1	KMT2A	NOTCH4	RET	TLR2
BAI3	CTNNA1	FLT3	KMT2C	NPM1	RHOH	TLR4
BAP1	CTNNB1	FLT4	KMT2D	NRAS	RICTOR	TLX1
BARD1	CUL3	FN1	KRAS	NSD1	RNASEL	TMEM216
BCL10	CYLD	FOXA1	LAMP1	NTRK1	RNF2	TMPRSS2
BCL11A	CYP2C19	FOXL2	LCK	NTRK2	RNF213	TNFAIP3
BCL11B	CYP2D6	FOXO1	LIFR	NTRK3	RNF43	TNFRSF14
BCL2	DAXX	FOXO3	LPHN3	NUMA1	ROS1	TNK2
BCL2L1	DCC	FOXP1	LPP	NUP214	RPL22	TOP1
BCL2L2	DDB2	FOXP4	LRP1B	NUP93	RPN1	TP53
BCL3	DDIT3	FUS	LTF	NUP98	RPS6KA2	ТРМ3
BCL6	DDR2	FZR1	LTK	PAK3	RPTOR	TPR
BCL9	DDX3X	G6PD	MAF	PALB2	RRM1	TRAF3
BCOR	DEK	GATA1	MAFB	PARP1	RUNX1	TRIM24
BCORL1	DICER1	GATA2	MAGEA1	PAX3	RUNX1T1	TRIM33
BCR	DIS3	GATA3	MAGI1	PAX5	SAMD9	TRIP11
BIRC2	DNAH9	GDNF	MALT1	PAX7	SBDS	TRRAP
BIRC3	DNMT3A	GID4	MAML2	PAX8	SDHA	TSC1
BIRC5	DOT1L	GNA11	MAP2K1	PBRM1	SDHB	TSC2
BLM	DPYD	GNA13	MAP2K2	PBX1	SDHC	TSHR
BLNK	DST	GNAI3	MAP2K4	PCDHAC2	SDHD	TYK2
BMPR1A	EGFR	GNAQ	MAP3K1	PDE4DIP	SEPT9	U2AF1
BOD1L1	EGR1	GNAS	MAP3K7	PDGFB	SETBP1	UBR5
BRAF	EML4	GPR124	MAPK1	PDGFRA	SETD2	UGT1A1
BRCA1	EP300	GPS2	MAPK8	PDGFRB	SF3B1	UMODL1
BRCA2	EP400	GRIN2A	MARK1	PDK1	SGK1	USP9X
BRD3	EPCAM	GRM8	MARK4	PER1	SH2B3	VHL
BRIP1	EPHA3	GSK3B	MBD1	PGAP3	SH2D1A	WAS
BTK	EPHA5	GUCY1A2	MCL1	PHF6	SMAD2	WHSC1
BUB1B	EPHA7	HCAR1	MDM2	PHLPP2	SMAD4	WISP3
C11orf30	EPHB1	HGF	MDM2	PHOX2B	SMARCA4	WRN
CACNA1E	EPHB4	HIF1A	MECOM	PIK3C2B	SMARCH4	WKN WT1
CALR	EPHB6	HIST1H1E	MECOM MED12	PIK3C3	SMC1A	XPA
CARD11	ERBB2	HLF	MED12 MEF2B	РІКЗСЗ РІКЗСА	SMCTA SMC3	XPA
CARDTT CASC5	ERBB3	HNF1A	MEF2B MEN1	РІКЗСА РІКЗСВ	SMC3	XPC XPO1
CASC3 CASP8						
1 1 1 0	ERBB4	HNRNPK	MET	PIK3CD	SMUG1	XRCC2

### TABLE AII Continued

ONTARIO PILOT PROFICIENCY TESTING FOR TUMOUR NGS PANELS, Spence et al.

CBL	ERCC2	HOXB13	MKL1	PIK3R1	SOCS1	ZNF217
CCND1	ERCC3	HRAS	MLF1	PIK3R2	SOCS3	ZNF384
CCND2	ERCC4	HSP90AA1	MLH1	PIM1	SOX10	ZNF521
CCND3	ERCC5	HSP90AB1	MLH3	PKD1L2	SOX11	ZNF703
CCNE1	ERG	ICK	MLLT1	PKHD1	SOX2	ZRSR2
CD74	ESR1	ID3	MLLT10	PLAG1	SP140	ZSWIM4
CD79A	ETS1	IDH1	MLLT3	PLCG1	SPEN	
CD79B	ETV1	IDH2	MLLT4	PLCG2	SPI1	
CDC73	ETV4	IGF1R	MMP2	PLEKHG5	SPOP	
CDH1	ETV5	IGF2	MN1	PML	SRC	
CDH11	ETV6	IGF2R	MNX1	PMS1	SRSF2	

### TABLE AII Continued

<sup>a</sup> Agilent, Santa Clara, CA, U.S.A. (used at the reference laboratory, Princess Margaret Cancer Centre, Toronto). UNH = University Health Network.