Quality Use of Pathology Program (QUPP) Final Report Prepared for the Commonwealth Department of Health

Project title: Developing an EQA to measure the Quality of Genomic Pathology Reports

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Title: Developing an EQA to measure the Quality of Genomic Pathology Reports

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Objective and Aims:

(1) *The* ***Objective*** *of the Activity is to provide the Department with a model that will autonomously analyse genomic pathology reports against a list of elements that are considered representative of best practice in text-based patient reports, and*

(2) *The* ***Aim*** *of the Activity is to develop scoring routine for text-based genomic reports using machine learning technology*.

For noting – The above-stated Aims/Objectives are not concerned with identifying individual laboratories or practitioners, but to develop system-level templates to allow the development of an effective and consistent communication channel for genetic pathology results. With the avalanche of genetic research and the advent new disease markers and innovation, this advance is vital to ensure rigorous but consistent reporting of complex results.

Executive Summary:

A standard for the reporting of genetic pathology results currently does not exist as a consensus, and often reflects an individual practitioner's preferences. While some excellent reports are produced, there is an overall a lack of consistency on which details to report or to emphasise. With genetics knowledge being so complex, poor and/or inconsistent reporting could make the translation of pathology results to patient welfare more challenging than necessary.

Glossary:

Abbreviation	Description
ACMG	American College of Medical Genetics
AI	Artificial Intelligence
AMP	Association for Molecular Pathology
ASCO	American Society of Clinical Oncology

Abbreviation	Description
CAP	College of American Pathologists
cDNA	Complementary DNA
CRC	Colorectal Carcinoma
EGFR	Epidermal Growth Factor receptor
EQA	External Quality Assessment
ESHG	European Society of Human Genetics
FFPE	Formalin-fixed, Paraffin-embedded
GPT	Generative Pre-Trained Transformers
HGNC	HUGO Gene Nomenclature Committee
HGVS	Human Genome Variation Society
NCBI	National Center for Biotechnology Information
NGS	Next Generation Sequencing
NPACC	National Pathology Accreditation Advisory Council
NSCLC	Non-small cell lung carcinoma
QA	Quality Assurance
QAP	Quality Assurance Program
R-CNN	Region-based Convolutional Neural Network
RCPAQAP	Royal College of Pathologists of Australasia Quality Assurance Programs
RPAH	Royal Prince Alfred Hospital
VAF	Variant Allele Frequency
VUS	Variant of Uncertain Significance

Period of activity:

Total Project (October 2022 - August 2023); Final Report (October 2023).

Scope of Work:

This document will report on the aims, subsequent research activities and results, as stated in the original *Funding Agreement* (2022), and in accord with any subsequent mutually agreed updates. As stated in the above agreements, the following activities were conducted and project aims achieved (Full details - Appendix A):

1. Compile, clean anonymised records - **(a)** Includes conversion of PDF to text (.txt) format pre-analysis, and **(b)** Decide on keywords and definitions, as per Best Practice standards – informed by scoping review of literature and RCPA experience (subsequently supported by text-mining).

2. Modelling of word patterns via text-mining and random forest pattern recognition algorithms - **(a)** For this activity random forest (RF) analyses were replaced by cluster analysis; **(b)** Develop and train machine learning model to identify key sections, and subsequently headings, of genetic pathology reports; **(c)** Develop scoring routines for reports.
3. Final reporting and evaluation.

Context: Previous reports produced in response to samples sent by the RCPAQAP for quality assurance purposes were compiled for word – text retrospective analyses to determine the variety of reporting styles, including text patterns and report formatting, with a focus on genetic aberrations associated with melanoma.

Changes and limitations experienced during the QUPP funding period:

ANU ethics review was required to allow the involvement of ANU staff (i.e., Lidbury). Since the QAP has ongoing ethics approval via the Royal Prince Alfred Hospital committee (RPAH, Sydney) for access to tissues samples for quality assurance (QA) purposes, it was expected that ANU approval would be automatic under the "Projects with Prior Approval" condition as stated in the NHMRC National Statement (Chapter 5.3). However, approximately 5-6 weeks elapsed before approval was granted (first enquiry 16th August 2022, final approval 27th September 2022 - communicated by committee Chair on the 5th October 2022).

The delay was due to the ANU Human Ethics Committee's (HREC) concern on participant consent to allow researcher access to their tissues. Ultimately, the HEC was convinced by the appropriate clauses of the NSW "Tissue Act" (1983), and our willingness to apply for a "Consent Waiver" for this project, which assured them that access to confidential patient information was impossible via their tissues and subsequent QAP reports (Consent Waiver document available upon request). The HREC was also insistent on the provision of original ethics documents submitted by the RCPAQAP to the RPAH committee some years earlier, which could not be located. However, in the end, approval was granted by the HREC Chair as a "Straightforward consent waiver – research arising from approved QA work with RPAH in Sydney". This situation led to the longer than anticipated delay in analysing QAP sample reports derived from anonymous tissue samples, which is key to achieving our stated project aims (initially communicated in December 2022, Performance Report 1).

(1) Introduction

The pathology report is the principal means of communication between the pathologist and the clinician. However, there are few published guidelines on reporting structure and heterogeneity in actual practice. A 2018 review of 16 US laboratories found wide variability in content, format and length both within individual laboratories and across different ones (1), and this reflects the situation in Australia.

The National Pathology Accreditation Advisory Council (NPAAC) sets the standards of medical pathology practice in Australia, and these should form the basis of quality assessment of any RCPAQAP program. The requirements for Genetic Pathology reports are described in their Tier 2 (Requirements for Pathology Services) and Tier 4 (Requirements for medical testing of human nucleic acids) documents (2, 3). While the latter document is in the process of revision as “Medical testing for human genetic variation standard”, the section on pathology reports is not expected to change significantly.

For cancer somatic variant testing, the most relevant requirements are listed below (Table 1). Both the American College of Medical Genetics (ACMG) and European Society of Human Genetics (ESHG) recommendations cover similar headings (4, 5).

TABLE 1: *The most relevant requirements to apply for thorough cancer somatic variant testing according to human/medical genetics societies from the US and Europe.*

Report requirements for cancer somatic variant testing according to the ACMG and ESHG - In order of report format
1. Identity of laboratories performing testing and issuing report, if different
2. Patient demographics (name, gender, age)
3. Unique identifier for each sample
4.Type of tissue tested and state (fresh, frozen, fixed)
5. Clinical details provided by referrer (history, purpose of testing)
6. Validated results i. Must unambiguously identify genetic loci being assayed and reference sequence used ii. Use of standard gene symbols and nomenclature from HGNC/HGVS/NCBI recommended. Common synonyms should not be the sole identifier. iii. Interpretation of biological significance of rare variants should be provided and must address clinical question
7. Must state in simple terms scope of analysis performed i. Coverage (targeted genes, exons, selected variants) ii. Methodology, limitations and relevant kit set specifications
8. Date and time of report release

Han *et al* (2017) performed formal scoring of lung cancer EFGR testing reports as part of a proficiency testing scheme (6). While their cohort showed improvement in performance from 2014 to 2016, recurrent errors in analytical and clinical interpretation were present. A similar RCPAQAP pilot project on assessing the quality of 2021 solid tumour genetics report is in progress, which scored reports based on the headings summarised in Table 2.

Clinical reporting of somatic variants in tumours is largely driven by underlying actionability. The AMP/ASCO/CAP has derived an evidence-based classification standard (7) as below (Fig. 1). In

addition, they recommended inclusion of sequencing depth and variant allele frequency (VAF) in reports. The ClinGen somatic working group has recently published as adjunct for assessment of novel variants, based on the ACMG germline classification guidelines (8). We do not expect laboratories to include adjunct classifications at this stage.

Somatic cancer variants are also curated in online databases (9). These contain information beyond the scope of individual pathology reports, but provide clinically relevant data headings.

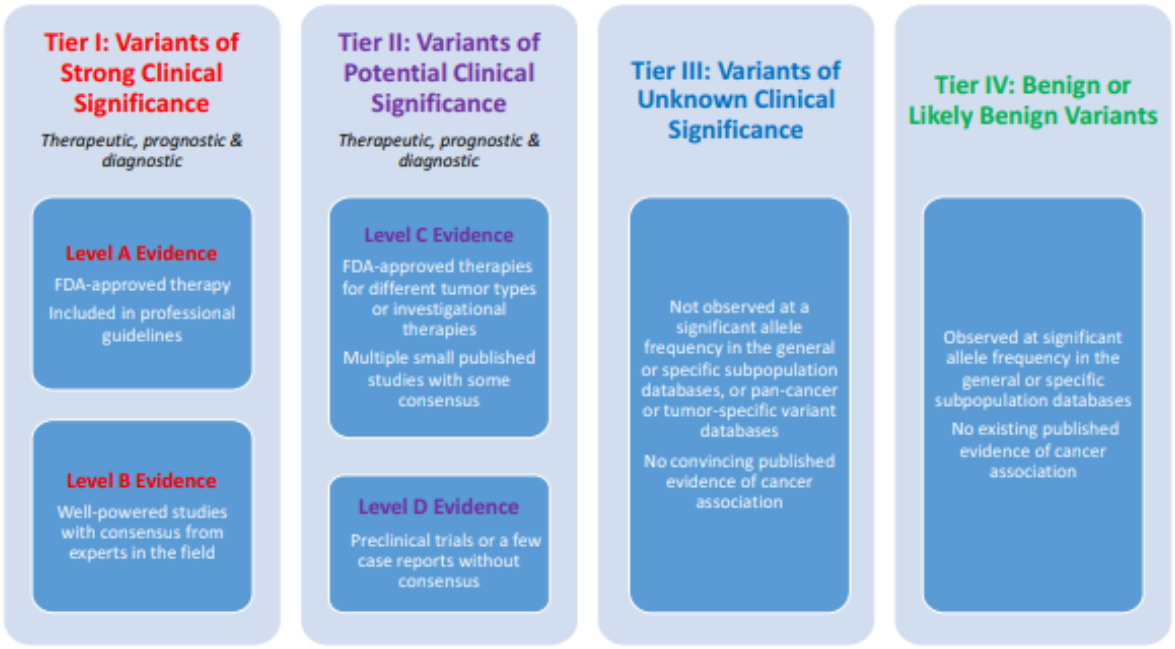


Figure 1: *ASCO/AMP/CAP clinical classification tiers for somatic cancer variants.(Conceived by Li et al. (7)).*

TABLE 2: *Headings utilised by the RCPAQAP to score solid tumour genetics reports (2021) while assessing report quality.*

Referrer name	Referrer contact details	Reporting lab logo/name
QA Program participant ID	Date sample received	QA Program sample ID
QA Program sample subset	Internal sample ID	Tumour site
Tumour type	Tissue type (FFPE)	Tissue form (slides/ribbon)
Tumour purity	Test requested by QAP	Test performed
List of genes tested	List of specific loci tested	Covers requested genes
Result	Genomic coordinates	Reference sequence
Reference sequence location	cDNA position	Protein change
Exon location	Correct diagnosis	Relevant negatives stated
Additional variants reported	Sequencing depth (NGS)	VAF (if NGS based)
Result summary	Variant description	Gene function
Protein domain	Predictive/prognostic value	Variant classification

Variant database cited	References cited	Instrument used
Limitations of method	Scientist responsible	Pathologist responsible
Stated as verified/complete	Completion date	Page numbering
	Errors	

Definitions: QAP (Quality Assurance Programme); NGS (Next-Generation Sequencing); FFPE (Formalin-fixed, Paraffin-embedded); VAF (Variant Allele Frequency).

(2) Methods

Data: A collection of 118 anonymous melanoma genetics reports submitted in April 2021 for the RCPAQAP Mutation Detection in Melanoma external quality assessment (EQA) program formed the text corpus for investigation, and represented reporting styles from private and public pathology departments from each Australian state and territory, and New Zealand, as well as the UK, Hong Kong and South Africa. As described above, full human ethics approval was granted under the established protocol in NSW, as well as by the ANU human research ethics committee (HREC) after some discussion (explained above).

Analysis: To achieve the aim of developing a standard report template to ensure the highest quality transmission of genetic pathology results, three strands of investigation were employed. They were -

(a) Narrative review and analysis of the field specific peer-reviewed academic and professional literature, as well as pertinent NPACC regulations, by a genetic pathologist;

(b) Text-mining supported by cluster algorithms to identify consistent word patterns within sample reports;

(c) Application of machine learning models to predict and identify document features;

Based on results from (a) - (c), then

(d) Establish a prototype report template to embed into pathology online reporting networks.

(a) Narrative Review

A literature search using internet services (PubMed, Google) and professional body (ACMG, NPAAC, ESHG) guidelines highlighted eight headings pertinent to best practice in genetic test reporting, summarised in Table 3. The headings were used to label targeted sections of participant reports for text mining and machine learning. Two key studies (1, 6) assessing reports using similar headings were identified and reviewed as a component of this investigation.

(b) Text-mining and clustering

From a corpus of 118 genetic pathology (melanoma) reports previously submitted to the RCPAQAP for quality assurance evaluation, word cluster patterns were detected via text mining (R statistical programming, "`tm`", "`cluster`", "`SnowballC`" etc packages), representing the most prominent word frequencies and associations (10, 11). These analyses allowed the detection of the most frequent words in the corpus, as well as cluster (association) patterns summarised by dendrogram and 2-dimensional cluster axes. With word (i.e., definition, heading, term) clusters identified, these were

aligned with the results of the narrative review (a) and used to populate the optimal format as derived from the machine learning investigations (c).

(c) Prototype report template

With reference to Tables 1 - 3 and Figure 1, establish report headings with cross-reference to text-mining results that identified common past report terms, words and definitions. Similarly refer to the narrative review results and text-mining to recommend sub-headings as well as questions to guide genetic pathology reporting. Once developed to this point, the resulting template will be validated by the results of report structure analyses as determined via Transformer models (Vaswani A. *et al,* 2023).

TABLE 3: *Eight report headings and attached information used to guide the genetic pathology narrative review of the literature by an expert pathologist (with reference to ACMG, NPAAC, ESHG guidelines).*

Heading	Relevant fields within
Administrative	Lab name, referrer, verification personnel, collection date, report date
Patient & sample information	Name, DOB, lab accession, sample type, histological diagnosis, % tumour content
Clinical question	Clinical history, test requested and indication
Result	HGVS nomenclature, reference sequence, genome built, VAF, sequencing depth
Interpretation	Gene function, variant effect, population data, literature evidence, classification
Recommendation	Treatment/further testing implications, clinical trials, literature evidence
Test scope & limitation	Methodology, limits of detection, target gene/variants
Summary	Succinct conclusion of findings

Supported by Makhnoon *et al* 2018 (1) and Han *et al* 2017 (6).

Model Selection and Validation Process:

- **(a)** Model Selection – The models chosen for assessment encompass Fast-RCNN, Fastr-RCNN, cascade-RCNN, LayoutLMv3, and LiLT (*Wang, J et al, 2022*). These models were selected as they are commonly used in document AI tasks and have demonstrated promising results in previous studies. All models chosen for assessment were previously finetuned against either the FUNSD (*G. Jaume et al, 2019*) or DocLayNet (*B. Pfitzmann et al, 2022*) Datasets.
- **(b)** Custom Dataset Preparation – Melanoma reports were imported into LabelStudio (*M.Tkachenko et all, 2020*) and manually labelled with bounding boxes for document layout and named entity recognition.

(c) Model Fine Tuning – To further enhance the models' performance and adaptability, they were subsequently fine-tuned against the custom labelled dataset. This custom dataset is specifically designed to address any shortcomings or specific requirements of the document AI tasks being performed.

(d) Model performance was then validated using the F1 Score (*SA Hicks et al, 2022*), a harmonic mean of precision and recall.

(3) Results – Project Activity Reports

The project results comprise three separate investigations (narrative review, text-mining, report formatting via AI), with the consolidation of results from these three themes contributing to the final outcome, namely, a standard reporting structure for genetic pathology (report template).

Narrative and manual report review:

Table 3 above summarises results from the narrative review of the guidelines and literature, and provides the basic heading structures and associated details. Under this rubric, solid tumour genetic pathology reports submitted for EQA modules at RCPAQAP were reviewed (Tables 4 and 5) using binary scoring of whether data from specific categories was present or absent. The manual review found significant inconsistency in reporting (Table 4). The best reported details (included in 100% of reports) were; *QA Program sample ID*, *Test performed*, and *Result*. Conversely, *Genomic coordinates*, *Protein domain* and *Variant database cited* were recorded in fewer than 25% of reports evaluated, with only <1% (14/655 reports) including *Genomic coordinates*. Furthermore, none of the reports provided the genome build used, which is necessary to interpret the genomic coordinates correctly.

χ^2 testing was used to look for differences in report quality across different times and laboratories. When looking at performance over time, only melanoma reports were examined to match the dataset used for machine-based learning assessment. Aside from feedback provided by standard assessment provided by RCPAQAP, EQA participants received no additional active intervention or education and we hypothesised the quality of the reports would remain largely unchanged. Indeed, for melanoma reports submitted in 2021, 2022 and 2023, there were no significant difference ($p < 0.05$) between the quality of reporting in 37 of 45 categories.

The 8 categories showing significant difference were inclusion of *QA sample subset*, *tissue type*, *test requested by referrer*, *tumour type*, *tumour site*, *associated therapy* and use of *variant database* and *references*. Individual reports were reviewed to try and identify the underlying cause for these differences.

In 2021, 2 of the 24 participating laboratories did not provide information on *associated therapy* and *literary references*. One of these laboratories only submitted instrument generated reports and did not re-participate in 2022 and 2023. The other laboratory participated EQA in 2021, 2022 and 2023, but only incorporated the information in their reports from mid 2022 onwards. Also, 4 glass sections

and 1 tissue ribbon sample was used in the EQA program in 2021. Tissue ribbon samples were not used in the other years and many laboratories failed to document this particular *tissue type* – it was only documented in 48% of reports in 2021, as opposed to 63-72% in the other years.

In 2022, only "melanoma" was given as the clinical history for 2 of the 4 EQA samples. This minimal history paradoxically led to a higher inclusion of *tumour type* and *tumour site* that year (86-93% compared to 61-79% other years). Two of the samples carried *RAS* mutations and were *BRAF* wildtype. At that time, *RAS* mutations had no associated therapy and many laboratories elected to include additional background information on *RAS variant descriptions* comments (57% vs 22-35% other years).

No convincing explanation were postulated for the difference in *QA sample subset* and *test requested by referrer*. The % inclusion were variable across all three years and did not show a continuous trend (92, 72, 82% for QA sample subset and 13, 25, 7% for test requested by referrer for 2021, 2022 and 2023 respectively).

The number of modules enrolled by laboratories were used as a surrogate for the size and possibly, expertise of individual laboratories. We compared the performance of laboratories enrolled in one module against laboratories enrolled in all nine modules over this period. Their performance differed in 22 out of 45 categories, and 9 module-laboratories performed better in 20 of these compared to 1 module-laboratories. The only two categories where 1 module-laboratories were superior were administrative only – the inclusion of their *laboratory name* and the *primary analyst*. The 9 module-laboratories used a variety of testing methods including next generation sequencing (NGS). On the other hand, none of the 1-module laboratories used NGS for their testing methods, explaining the total discordance in *VAF* and *sequencing depth* comparisons. These results were only possible using NGS.

Text-mining and clustering:

Via R statistical programming, text analyses of a RCPAQAP melanoma report corpus (n = 118 separate reports) was achieved through text-mining algorithms and supporting cluster methods. For the evaluation of word consistency, the reports were randomly divided into three sub-groups for primary investigation and subsequently analysed as an entire combined corpus. The resulting word frequencies and associations are summarised in Table 6.

Results were generally consistent across individual sub-groups, and were divided into strong, moderate or weak cluster associations. The strongest were patterns of common words expected from a report – for example, "collect", "refer", "clinic", "sample", with scattered context words (e.g., "tumour"). Such contextual words, e.g., "clinic", overlapped with the moderate cluster group, while others were unique to this class as more specialised terms ("sequence", "gene"). "Melanoma" featured for the moderate and weak classes. The weakest cluster associations were highly technical terms focussed on the tumour, namely, the key mutation, BRAF, supported by reference to "mutation" and "variants". Interestingly, NRAS did not feature at sufficient frequency.

Table 6 results were derived from cluster plots and dendrograms generated from the analysis of the entire melanoma corpus (Figures 2 a-b), with word frequency summarised by Figure 3. The separate Group results (A, B & C) are presented in Appendix B.

Figure 2a presents word clusters via a dendrogram format, with word cluster distance (d) on the x-axis and the measure of similarity (Height) on the y-axis, while Figure 2b displays the same results as a component 1 versus 2 cluster plots. Figure 2b shows dense word clustering for cluster 2, with the least density for cluster 1. Inspection of the Figure 2a shows words like “patient”, “type”, “use” and “result” (red boxes) as ranging at less than 50 to less than 20 on the Height scale, indicating tight associations between those and other terms clustered nearby. Alternatively, cluster 1 comprises “BRAF”, “mutat(ion)” and “variant” with height and distance showing greater Euclidian distance between these terms, which as indicated (Table 6), is related to specialist genetic terminology. The “mutant”, “BRAF”, “melanoma” relationship (blue box - Figure 2a) is illustrative of this point, with greater specialisation linked to sparser associations.

TABLE 4: *Results from an RCPAQAP pilot study (unpublished data) summarising variable quality within reporting categories (pages 14 – 15).*

Reporting Criteria & Details Assessed	CRC 2021 (n=119)		CRC 2022 (n=88)		Glioma 2021 (n=39)		Glioma 2022 (n=46)		Lung cancer 2021 (n=119)		Lung cancer 2022 (n=89)		Melanoma 2021 (n=118)		Melanoma 2022 (n=89)		Melanoma 2023 first half (n=38)	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Participant ID	49	70	31	55	15	24	24	22	44	75	27	62	55	63	35	54	22	16
QA sample	14	105	32	54	9	30	15	31	25	94	24	65	30	88	19	70	12	26
Referrer details	39	80	22	64	12	27	14	32	25	94	34	55	25	93	29	60	10	28
Date received	30	89	18	68	6	33	2	44	20	99	12	77	20	98	12	77	6	32
QA sample ID	0	119	0	86	0	39	0	46	0	119	0	89	0	118	0	89	0	38
QA samp. subset	31	65	33	53	12	27	20	26	19	76	35	54	8	88	25	64	7	31
Internal lab ID	35	84	18	68	9	30	8	38	20	99	10	79	20	98	9	80	5	33
Tissue state (FFPE)	19	100	20	66	15	24	6	40	29	90	19	70	36	82	24	65	8	30
Tissue type	60	59	28	46	24	15	20	26	66	53	29	48	61	57	19	50	14	24
Test requested	90	29	70	16	24	15	36	10	89	30	71	18	103	15	67	22	35	3
Tumour type	10	109	8	78	3	36	8	38	29	90	4	85	25	93	6	83	8	30
Tumour site	23	78	23	63	9	30	9	26	35	60	7	16	37	59	6	38	13	25
Tumour purity	9	87	10	76	6	33	10	36	8	87	8	81	13	83	6	83	8	30
Test performed	0	119	0	86	0	39	0	34	0	119	0	89	0	118	0	89	0	38
Instrument	14	105	4	82	24	15	4	30	10	109	6	83	13	105	8	81	2	36
Gene targets	5	114	2	84	0	39	0	34	0	119	0	89	5	113	0	89	0	38
Intragene targets	16	103	10	76	6	33	12	22	15	104	10	79	15	103	15	74	6	32
Result summary	10	109	0	86	0	39	0	34	10	109	0	89	5	113	0	89	0	38
Additional variants	31	24	6	19	12	6	1	14	31	14	11	13	54	16	32	17	11	8
Sequencing depth	25	25	18	18	6	8	10	9	20	25	18	20	37	19	32	19	10	9
VAF	1	49	1	35	0	14	3	17	9	34	2	36	8	38	4	47	2	17
Result	0	116	0	61	0	26	0	24	0	90	0	76	0	87	0	86	0	37
Relevant negatives	26	93	11	69	9	24	14	20	1	45	7	48	17	75	15	44	10	14
Correct diagnosis	1	118	3	83	6	33	0	34	3	116	3	86	7	111	0	89	1	37
Gene coordinates	116	0	86	0	24	0	31	3	90	0	87	1	88	4	84	4	35	2
Ref sequence	28	88	13	48	0	28	2	22	14	90	21	58	12	81	18	66	2	35
Ref seq in results	35	58	9	39	9	19	6	16	56	41	18	39	34	47	25	42	9	26
cDNA change	6	110	1	59	0	24	0	24	5	85	2	55	7	80	2	67	3	34
Protein change	4	112	2	58	2	22	1	23	0	90	0	57	2	85	0	70	0	37
Exon location	64	52	38	22	22	5	23	1	48	42	17	57	65	23	59	11	30	7

Reporting Criteria & Details Assessed	CRC 2021 (n=119)		CRC 2022 (n=88)		Glioma 2021 (n=39)		Glioma 2022 (n=46)		Lung cancer 2021 (n=119)		Lung cancer 2022 (n=89)		Melanoma 2021 (n=118)		Melanoma 2022 (n=89)		Melanoma 2023 first half (n=38)	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Variant class	91	25	46	18	24	7	16	9	65	25	64	14	65	22	62	24	26	11
Associated therapy	4	114	3	78	0	39	0	34	0	119	2	85	11	104	0	86	0	37
Variant description	95	21	24	40	28	7	16	14	71	19	38	40	67	20	32	42	24	13
Gene function	105	11	57	7	24	11	21	9	78	13	67	11	76	12	63	11	35	2
Protein domain	111	5	59	4	33	2	26	4	82	8	72	6	75	12	69	5	36	1
Variant database	101	15	49	14	32	3	25	5	72	18	68	10	85	10	66	8	32	5
References	9	109	5	79	3	36	8	38	0	119	4	85	19	97	7	81	0	37
Limitations	10	109	9	76	3	36	4	42	5	114	4	85	14	104	4	85	1	37
Primary analyst	84	35	57	28	30	9	25	21	94	25	64	25	88	30	62	27	28	10
Sign - pathologist	49	70	31	54	21	18	16	30	50	69	32	57	34	84	32	57	13	25
Report status	30	89	17	68	9	30	4	42	30	89	12	77	33	85	16	73	8	30
Page numbering	30	89	17	68	12	27	10	36	35	84	22	67	24	94	24	65	8	30
Complete date	45	74	21	64	6	33	10	36	40	79	18	71	38	80	22	67	10	28
Reporting lab	45	74	27	58	15	24	22	24	55	64	31	58	29	89	35	54	12	26
Error	108	11	80	8	36	3	33	13	107	12	83	6	108	10	81	8	38	0

655 reports from nine EQA surveys collected between April 2021 to April 2023 were available. 45 categories were reviewed, grouped according to headings provided in Table 3. The sum of reports where categories were present/absent would not match the total when these were irrelevant in the context of the result, such as cDNA or protein changes when no mutation was present. Absolute counts were provided to facilitate comparison by X^2 testing (Table 5). *Error* was a reverse coded category where absence reflected good performance.

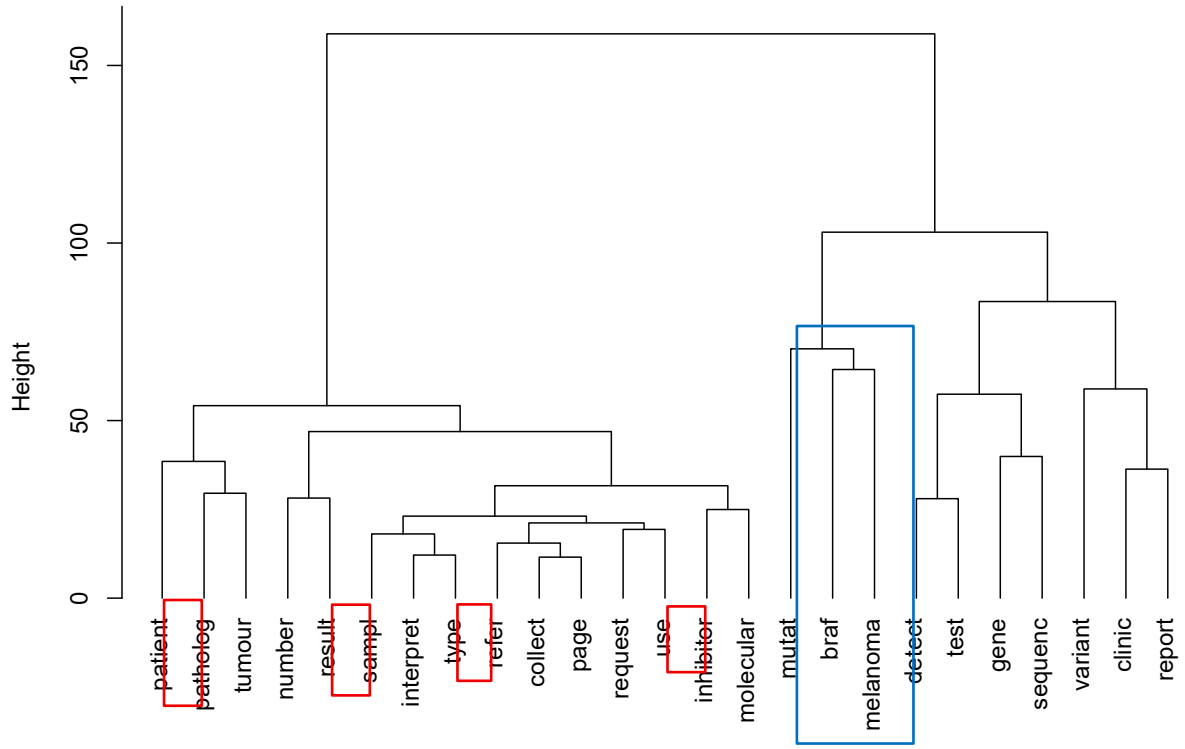
A significant difference between comparison groups is represented by a *p*-value ≤ 0.05. The quality of melanoma testing reports in 2021, 2022 and 2023 showed differences in only 8 categories. Possible explanations were provided in the discussion above. Conversely, differences exist in 20 categories between laboratories enrolled in only one EQA module and those enrolled in all nine available modules over the same period.

TABLE 5: *χ^2 test comparing (1) Performance of melanoma testing EQA results between 2021-23 and (2) Laboratories enrolled in one module versus all nine modules over the same period.*

Report Criteria	Melanoma reports 2021, 2022, 2023		1 enrolment labs vs 9 enrolment labs	
	c^2 statistic	*p*-value	c^2 statistic	*p*-value
Participant ID	3.77	0.15	14.87	<0.005
QA sample stated	1.52	0.47	0.56	0.46
Referrer details	3.42	0.18	15.43	<0.005
Date received	0.47	0.79	17.92	<0.005
QA sample ID	Total concordance		Total concordance	
QA sample subset	12.25	<0.005	0.2	0.66
Internal lab ID	2.00	0.37	33.14	<0.005
Tissue state (FFPE)	1.33	0.52	1.89	0.17
Tissue type	10.91	<0.005	2.19	0.14
Test requested	7.69	0.02	0.25	0.62
Tumour type	8.79	0.01	72	<0.005
Tumour site	8.85	0.01	29.16	<0.005
Tumour purity	5.45	0.07	70.1	<0.005
Test performed	Total concordance		Total concordance	
Instrument	1.14	0.56	1.49	0.22
Gene targets	5.49	0.06	33.53	<0.005
Intragene targets	0.74	0.69	2.54	0.11
Result summary	5.49	0.06	4.18	<0.005
Additional variants	3.55	0.17	16.77	<0.005
Sequencing depth	1.10	0.58	Total discordance	
VAF	2.13	0.34	Total discordance	
Result	Total concordance		Total concordance	
Relevant negatives	5.71	0.06	0.01	0.91
Correct diagnosis	5.71	0.06	3.3	0.07
Gene coordinates	0.07	0.97	0.91	0.34
Ref sequence	5.73	0.06	13.98	<0.005
Ref seq in results	2.77	0.25	21.45	<0.005
cDNA change	2.03	0.36	20.29	<0.005
Protein change	2.49	0.29	1.1	0.29
Exon location	2.67	0.26	0.19	0.67
Variant class	0.30	0.86	29.65	<0.005

Report Criteria	Melanoma reports 2021, 2022, 2023		1 enrolment labs vs 9 enrolment labs	
	c^2 statistic	*p*-value	c^2 statistic	*p*-value
Associated therapy	12.34	<0.005	50.36	<0.005
Variant description	19.52	<0.005	1.95	0.16
Gene function	2.17	0.34	12.88	<0.005
Protein domain	4.64	0.10	5.14	0.02
Variant database	0.25	0.88	10	<0.005
References	8.98	0.01	61.98	<0.005
Limitations	5.50	0.06	3.69	0.055
Primary analyst	0.64	0.73	33.64	<0.005
Signing pathologist	1.26	0.53	0.43	0.51
Report status	2.96	0.23	3.69	0.055
Page numbering	1.35	0.51	2.65	0.10
Complete date	1.50	0.47	0	0.97
Reporting lab	5.16	0.08	10.25	<0.005
Error	3.59	0.17	3.05	0.08

(a)



Distance (d)

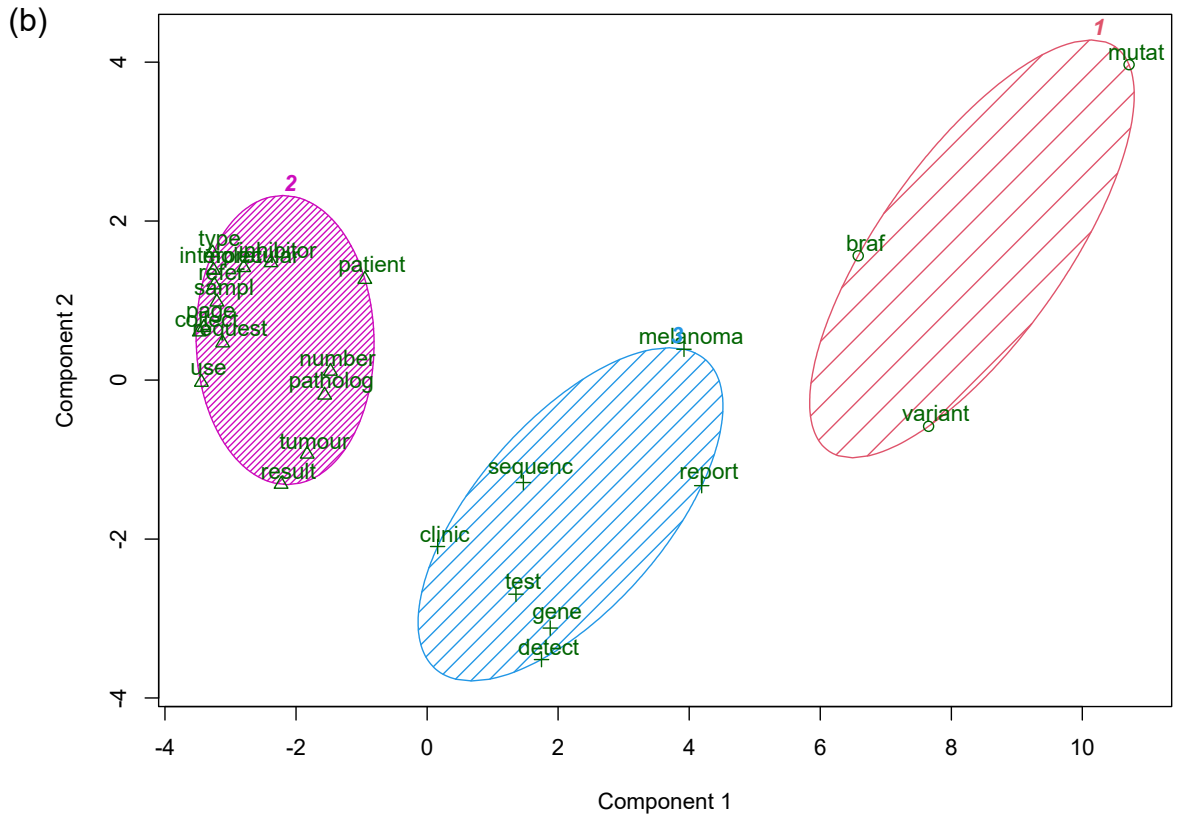


Figure 2: ***(a)*** *Dendrogram presentation of word clusters detected in 118 melanoma genetics reports previously submitted to the RCPAQAP for quality assurance purposes* ***(b)*** *The same results as for (a) but presented as two-dimensional clustering patterns (71.54% point variability explained).*

TABLE 6: *Strongest to weakest word clusters found in previously submitted RCPAQAP Melanoma reports (n = 118), as informed by text clustering analyses. The report sample was divided randomly into approximately equal sub-groups (Groups A, B, C) prior to analysis, and investigated individually and finally as a combined total sample.*

Report Group Analysed	**Strongest Associations**	**Moderate Associations**	**Weakest Associations**
Group A	Collect Refer Inhibitor Sample Tumour Clinic Number Result Metastat(ic) Interpret Page Molecular	Report Test Detect (Variant)	BRAF Mutat(ion) Melanoma
Group B	Molecular Interpret Inhibitor Number Result Patient Sampl(e) Type Receiv(e) Request Refer Dob (date of birth) Collect Page	Melanoma Sequence Clinic Gene Test Detect	BRAF Mutat(ion) Variant Report
Group C	Type Patient Tumour Number Result Collect Request	Sequence Melanoma Report Clinic Test Detect Gene	BRAF Mutat(ion) Variant

Report Group Analysed	Strongest Associations	Moderate Associations	Weakest Associations
	Inhibitor Interpret		
Groups ABC	Type Patient Tumour Number Result Collect Request Inhibitor Interpret Patholog(y) Sampl(e) Refer Molecular	Sequence Melanoma Report Clinic Test Detect Gene	BRAF Mutat(ion) Variant

As well as clusters (Figures 2a.b), word frequency (count of individual words within the total corpus of 118 reports) was assessed (Figure 3).

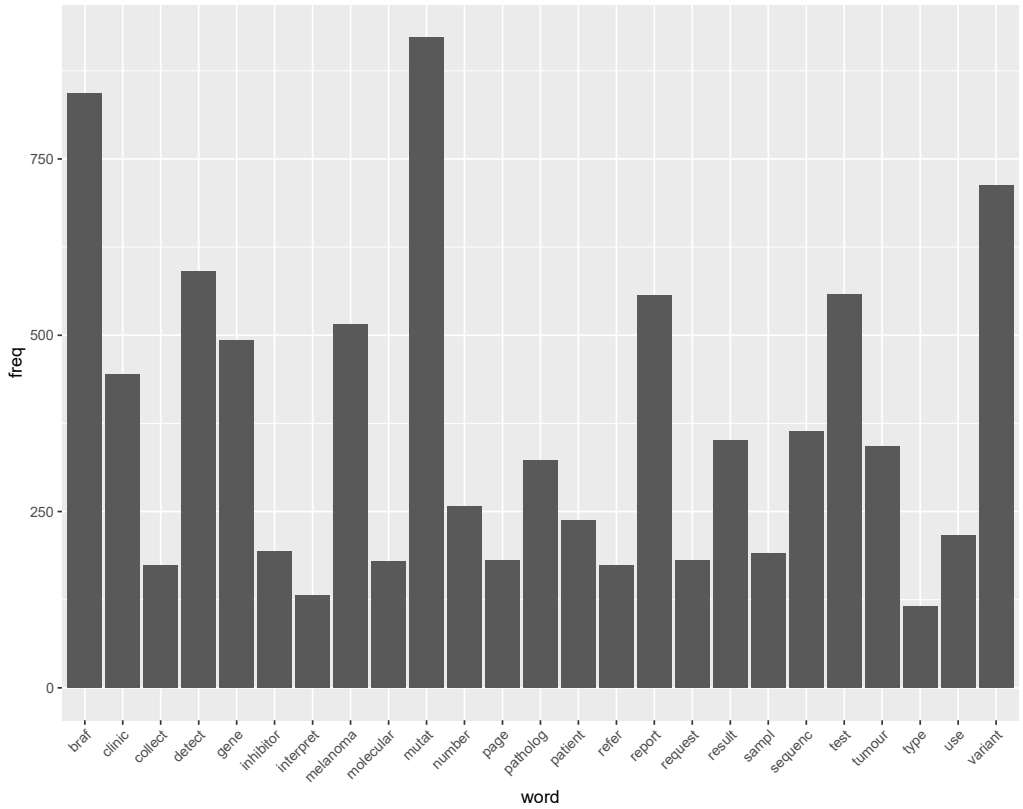


Figure 3: *Individual word frequencies found in the corpus of 118 individual RCPAQAP melanoma reports (Groups A, B & C) previously submitted for quality assurance evaluation. Only words with a frequency of > 150 were included.*

The most frequent words (in order) for the melanoma corpus were; “mutat..”, “BRAF” (> 750 occurrences), “variant”, “detect”, “report”, “test”, “melanoma”, (> 500 occurrences). Other words with a frequency > 150 appearances were emblematic of genetic and molecular investigations in the medical context, such as “gene”, “inhibitor”, “sequence”, “clinic”, “result”.

From 118 reports, 12 did not mention the primary gene of interest, “BRAF”, with 9/12 incidences due to incomplete or failed PDF to text (.txt) scans, and the three others stating either “No mutation detected”, or only reported NRAS and/or other melanoma associated genes. On cross-checking the original PDF reports, the 9 empty scans did mention BRAF in text. The frequency of BRAF when stated in reports (n = 106) ranged from 1 to 16 separate occurrences per report, reflecting the range of analytical depth applied by the various laboratories.

The word frequency results (Figure 3) suggest an interesting feature of these reports. BRAF for example, is the second most frequent word in the examined corpus, which makes sense as the leading gene of interest in melanoma. However, as found via cluster analysis the association with other specialised genetics terms was there, but not as strongly as found for other common report terms. Taking the 106 reports that featured BRAF, at an estimated total frequency of 800, proposes an average of approximately 7.5 occurrences per report (which agrees with the calculated *median* BRAF frequency of 7.0 and *mean* of 7.14 per report). This suggests that while BRAF is a frequent word, it does not fit a regular pattern within the structure of the reports analysed.

Model Selection and validation:

Model selection and validation are significant stages in any machine learning process, more so for complex tasks such as Document Artificial Intelligence (AI). Document AI primarily involves tasks like layout detection, form parsing, and Named Entity Recognition (NER) which determine the structure, content and relevance of information in a document. This article will delve into the process of model selection – the comparative analysis of model capabilities and the validation process which determines the accuracy, precision, and overall performance of chosen models.

To illustrate the model selection and validation process, we focus on five models – Fast-RCNN, Fastr-RCNN, cascade-RCNN, LayoutLMv3, and LiLT. These models were fine-tuned on the 'docLay' dataset, a dataset that primarily focuses on document layout analysis. Following the initial fine-tuning, the models were further finetuned on a custom-labelled dataset, created exclusively to meet the unique needs of our project.

Fast-RCNN, Fastr-RCNN, and cascade-RCNN are all variants of the Region-CNN (RCNN) model that uses region proposals to identify objects within an image, in this case, components within a document for layout detection. Fast-RCNN improves upon the RCNN model by introducing a Region of Interest (RoI) pooling layer and adding a fully connected layer after it. Fastr-RCNN takes it a step further by including an additional Region Proposal Network (RPN) stage for generating object proposals. Cascade-RCNN introduces cascading stages in the RCNN architecture to enhance the localisation capacity of the model.

LayoutLMv3 and LiLT, on the other hand, are transformer-based models that consider both the textual content and positional information of the components for document understanding. LayoutLMv3 builds on the LayoutLM model by adding improved positional embeddings while LiLT uses a language-independent approach, incorporating Bi-Directional Attention Complementation (BiACM), and self-supervised pre-training tasks to improve joint text-layout understanding.

A primary aspect to consider in model selection is the performance of these models. In this case, the Fast-RCNN, Fastr-RCNN, and the cascade-RCNN models suffered from poor performance. While they offer some beneficial aspects like the capacity for object detection and localisation, they fall short when handling complex document layouts which require careful analysis of both text and positional information. They were unable to efficiently analyse and differentiate between multiple components with similar characteristics within a document.

LayoutLMv3 and LiLT had superior performance outcomes compared to the RCNN variants. These models, with their advanced understanding of the relevance of text and layout, were more adept at identifying, categorising, and analysing document structure and content. However, it is also essential to consider licensing restrictions when selecting a model. LayoutLMv3 is under the restrictive Creative Commons License CC BY-NC-SA 4.0, which limits the use of this model for commercial purposes. In contrast, the LiLT model carries an MIT license, which offers broad permissions including for commercial use, making it a more viable choice for wide-ranging applications.

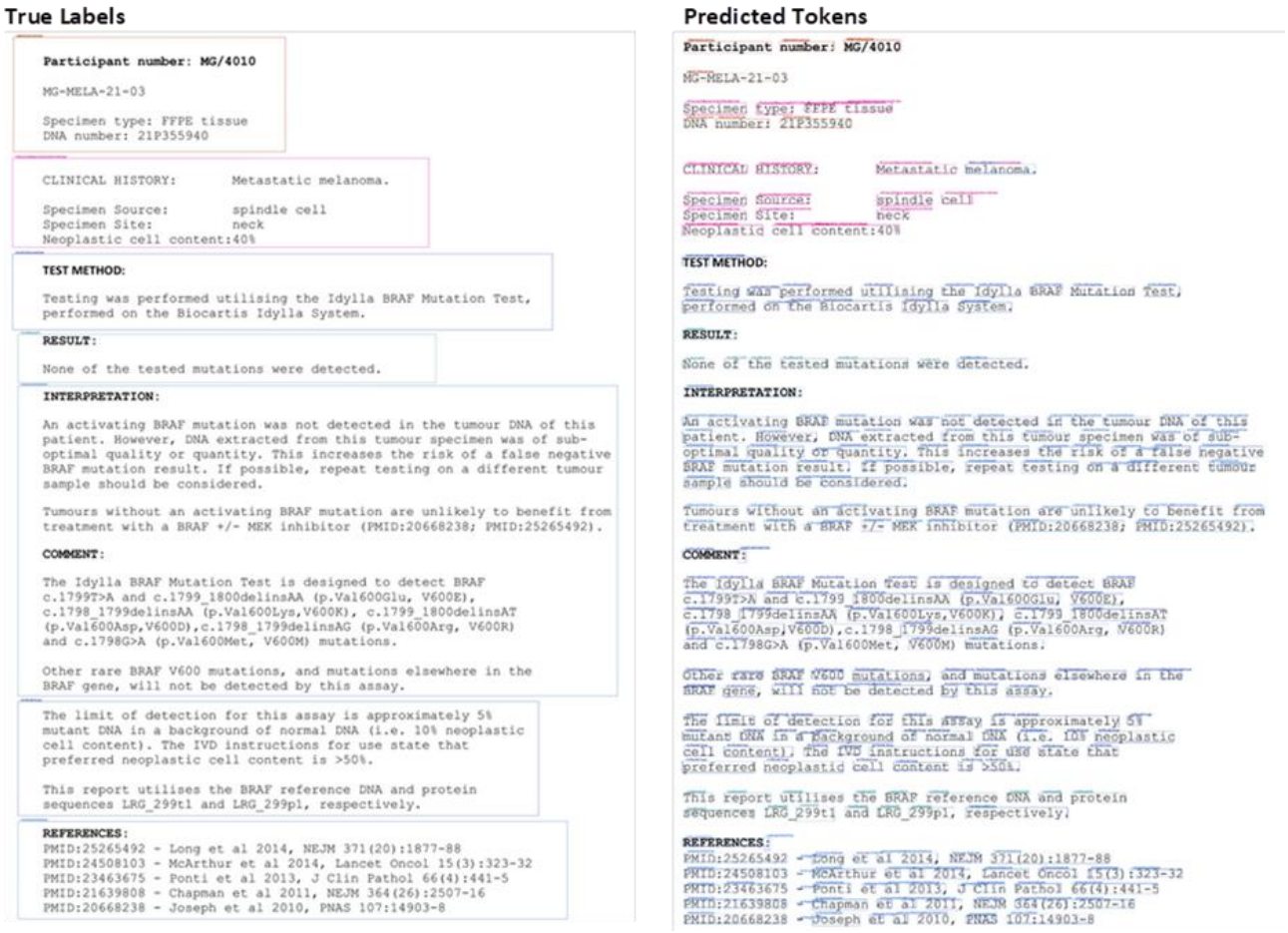


Figure 5: *Side by side comparison of an example document for the document Layout task. Left the true labelled document, Right the predicted token classes.*

During model validation, the performance metrics of the chosen models are assessed. For our task, the primary metric was the F1 score, a harmonic mean of precision and recall, which gives a better measure of the incorrectly classified cases than the accuracy metric. For the task of document layout detection, the LiLT model achieved an impressive F1 score of 0.75. For Named Entity Recognition (NER), a task that identifies entities of interest within the text, the LiLT model scored above 0.9 on the Layout Detection task.

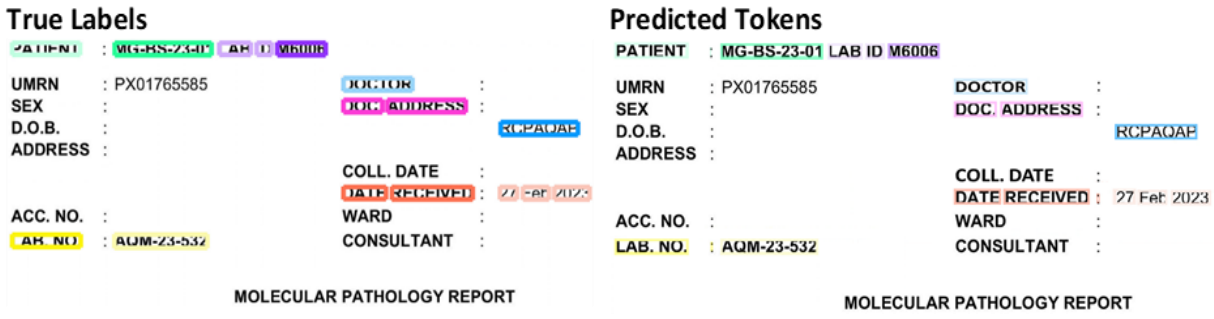


Figure 6: *Side by side comparison of an example document for NER on a given report section. Left the true labelled document, Right the predicted token classes.*

The high scores on these validation metrics indicate the LiLT model is adequately optimised to balance precision and recall, making it an effective tool for structured document understanding tasks. These validation results further cement the choice of the LiLT model over the others for tasks of document layout detection and NER.

Genetic Pathology Report Template:

Based on the results from (a) narrative reviews, (b) text-mining and clustering, and (c) GPT field analyses, the proposed report structure and content are as follows (Tables 8 and 9).

Table 8 summarises administrative headings in relation to terms identified via narrative review investigations by a genetic pathology expert and text-clustering, while Table 9 takes this model template further to a final recommendation of a genetic reporting structure after the addition of insights from Named Entity Recognition (NER) and associated form field analyses. Table 9 represents the final, standard genetic reporting tool recommended by this project.

The recommended genetic reporting template was the result of both subjective (expert) and objective (text-mining, NER) methods ultimately combined to produce a reporting structure supported by evidence obtained via melanoma reports previously submitted to the RCPAQAP.

TABLE 8: *Proposed genetic pathology report template modified from the eight report headings and attached information used to guide the genetic pathology narrative review of the literature by an expert pathologist (with reference to Table 3), with cross-referencing to word clusters identified by text-mining (Table 6 and Figures 2 - 3).*

Heading	Terms - Headings (Narrative)	Terms - Headings (Text-Clusters)
Administrative	Lab name, referrer, verification personnel, collection date, report date	Patient, *Collect,* Request, *Refer*
Patient & sample information	Name, DOB, lab accession, sample type, histological diagnosis, % tumour content	*Patient, Tumour*, Inhibitor, *Sample*, *Type*, Molecular
Clinical question	Clinical history, test requested and indication	Sequence, *Report*, *Clinic*, *Test*, Detect, Gene Melanoma (or tumour of interest)
Result	HGVS nomenclature, reference sequence, genome built, VAF, sequencing depth	BRAF, Mutation, Variant, *Sequence*, Detect, *Gene*, Report, Clinic(al), (Melanoma)
Interpretation	Gene function, variant effect, population data, literature evidence, classification	BRAF, Mutation, *Variant*, Report, Clinic, *Gene*, Test, Detect, Sequence (Melanoma)
Recommendation	Treatment/further testing implications, clinical trials, literature evidence	Sequence, Clinic, Gene, Test, Detect (Melanoma)
Test scope & limitation	Methodology, limits of detection, target gene/variants	BRAF, NRAS (minimum)
Summary	Succinct conclusion of findings	Selection from all clusters - Type, tumour, molecular, gene …

Italicised text - Common words detected by narrative review and text clusters;

Underlined text - Suggestions for additional words, terms, headings.

TABLE 9: *Final genetic reporting template derived from previous melanoma report (n = 118) analyses.*

Major Report Heading	**Information Required**
Administrative	Lab name, referrer, verification personnel, collection (Request) date, report date
Patient & sample information	
Clinical question	
Result *	Reference sequence and database Specific gene tests Depth of sequencing BRAF - (Yes/No) Other Gene(s) - (Yes/No) If Yes: Mutation, Variant, Sequence detected
Interpretation	Tumour Gene/Sequence detected Variant and effects Sequence/Gene/Protein function Classification Population data Supporting literature (including mention of gene databases)
Recommendation	
Test scope & limitation	BRAF, NRAS (minimum)
Summary	Tissue sample collected - gross description and histology Clinical inferences Sample preparation Sequencing method Supporting database

Major Report Heading	Information Required
	Gene/sequence detected Prognosis suggested by mutation
Footnotes	* Report as NPAAC nomenclature

(4) Conclusions and Discussion

The genetic pathology reporting template presented was designed according to evidence gathered from a combination of pathologist expertise and agnostic machine learning methods, namely, text patterns and formatting structures. While the narrative review by a pathology expert considered several cancer examples for guidance (1,4,5-9), the machine learning text and structure investigations relied upon genetic pathology reports concerning melanoma only (n = 118). Therefore, whether the results reported herein can be generalised to the reporting of genetics for other conditions will need further consideration. A RCPAQAP study on this topic that commenced in 2021 is ongoing, and will provide further insights into Australian genetic reporting (solid tumours) in future (Table 2).

Interest in genetic reporting has attracted prior scholarly attention, and helps to inform current regulation via bodies like NPAAC (2,3). The study by Han *et al*. evaluated genetic pathology reporting (EGFR mutation) for invited laboratories and compared 53 examples each from 2014 (N = 74) and 2016 (N = 231), with improvements in reporting noted when 2016 was compared with 2014 (6). The Han *et al*. investigation was particularly valuable since it developed discrete metrics and evaluation criteria to score reports, and therefore identify broader quality trends under specific report headings (e.g., “Anatomical origin of sample”). Identified as in need of particular attention was the reporting of “molecular diagnosis”, as well as poor adherence to HGVS nomenclature (5 - 9). Examples of poor nomenclature practice included, “ … improper description of nucleotide change”, “ … absence of nucleotide change (e.g., “L858R, wild-type”), “ … incomplete description of an undefined deletion or insertion”. Other issues identified within the genetic reporting domain include; lack of guidelines for VUS reporting (1); alignment with ISO15189 standards recommended to assist reporting (5); suggestion of a four-tier system of classification (7 - see Figure 1). Some publications suggest a range of databases, either existing or developed by them, as reference tools to support contemporary genetics interpretation and reporting (7 - 9).

(5) Future Research:

The results presented were drawn from investigations of melanoma reports previously submitted the RCPAQAP for quality assurance monitoring. Future studies will similarly evaluate reports for other tumours submitted to the RCPAQAP under the EQA requirements. Other tumour examples available via the RCPAQAP are colorectal, non-small cell lung carcinoma, and glioma.

From an analytical perspective, further development of GPT tools and associated algorithms that allow the investigation of text/heading structures, with reference to the vast array of reporting structures available via the world-wide web, will further promote our capacity to synthesise evidence and apply this to a range of tasks, including additional research into the objective pursued within this project.

The immediate follow up task is to apply the reporting rubric constructed for melanoma to other tumour types, and assess whether the melanoma format is generalisable. It can be expected that the basic administrative headings and attached details will remain consistent between tumour types,

but in light of ever-expanding research into human genetics the scientific and technical aspects of the reporting structure will require flexibility to accommodate advances in the field. One can speculate that in the not-too-distant future epigenetic features associated directly with tumours, or tumour suppressors - enhancers, will require space and consideration within reporting structures. Technological advances in computing and the molecular acuity of abnormality detection in DNA and RNA samples will very likely to continue at a rapid rate, and likewise, will require accommodation within reporting structures.

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(7) Appendices:

Appendix (A)

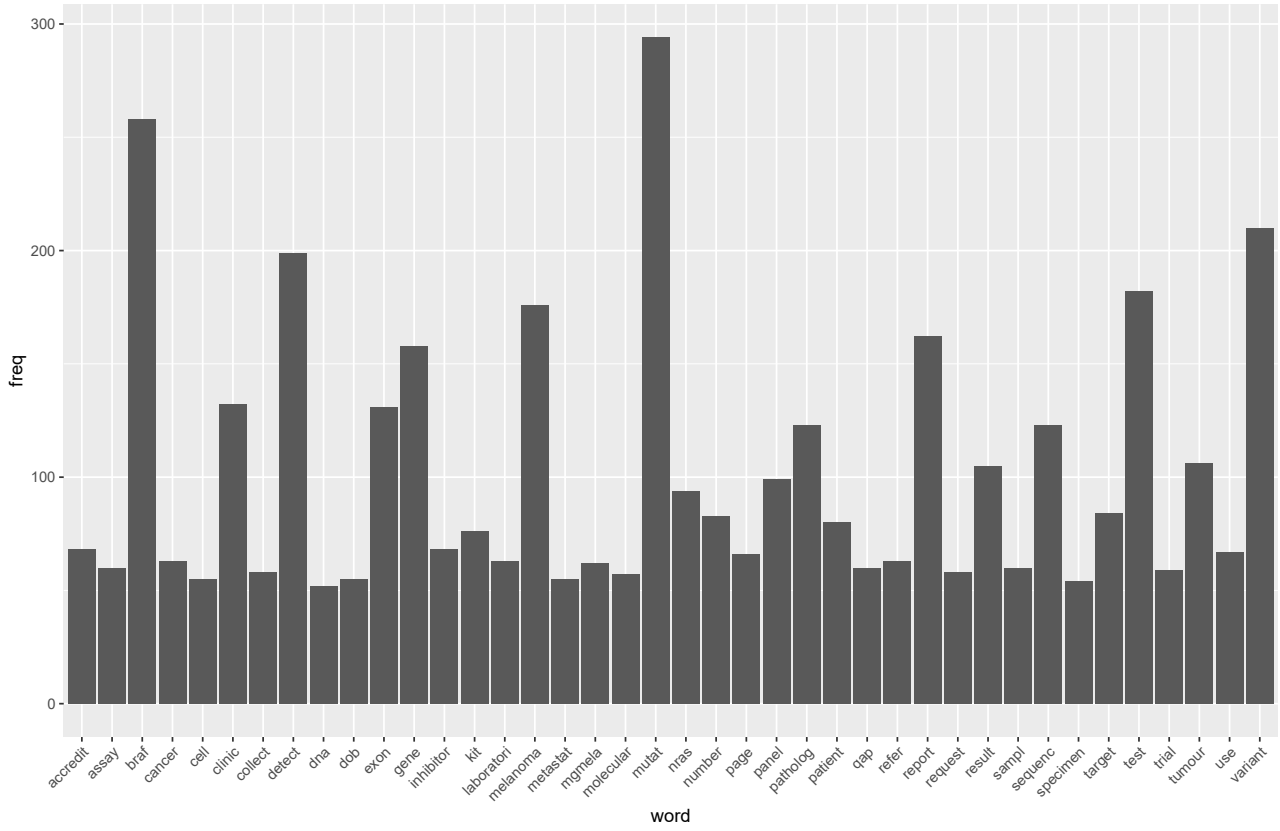
Summary - Evaluation of the Activity against the Performance Indicators

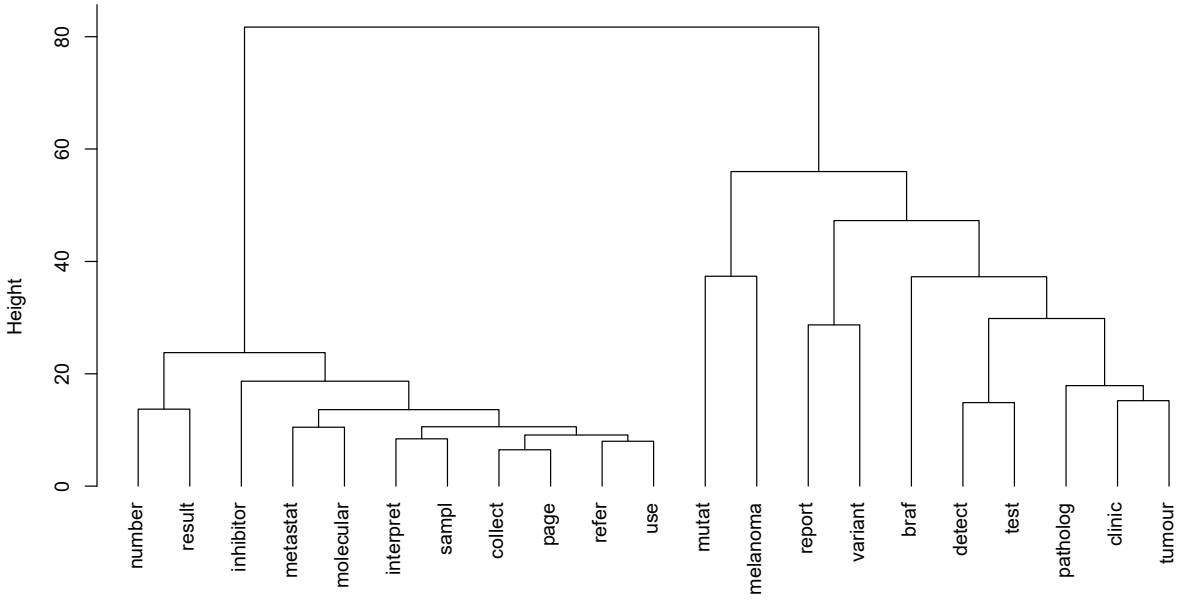
What are the key milestones for this project that will identify that you have achieved the objectives of the project?	**Milestone Status: Dec 2022 – August 2023**
1a. Compile, clean anonymised records. Convert PDF to text (.txt) format pre-analysis. 1b. Decide on keywords and definitions, as per Best Practice standards – informed by scoping review of literature and RCPA experience.	1a. Achieved. 1b. All data compiled, cleaned and pattern rules designed post keywords and definitions established.
2a. Modelling of (1) with text-mining and random forest pattern recognition algorithms 2b. Integrate machine learning software into routine Labware software routines. 2c. Develop scoring routines for reports.	2a. Achieved (NB. Random forest replaced by cluster analyses). 2b. Partly achieved (Machine learning model developed and trained to identify key sections of genetic pathology reports). 2c. Achieved
3. Final reporting and evaluation. (Publish results and findings in peer-reviewed journals and other literature)	3. Partly achieved (Final report completed; Publication pending)

Appendix (B)

Frequency, Dendrogram and Cluster plots for separate Group A, B or C tranches taken from the entire corpus of 118 melanoma reports. In-text results report the combined Group A-C analysis.

Group A:





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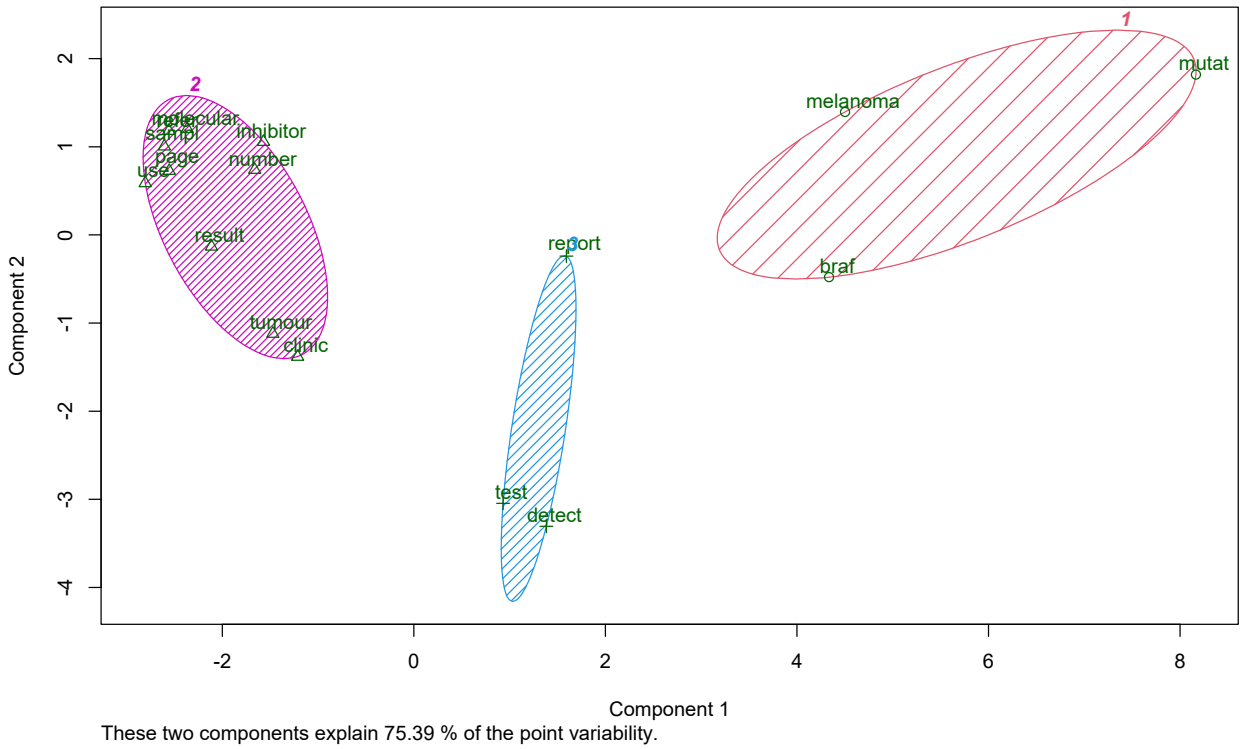
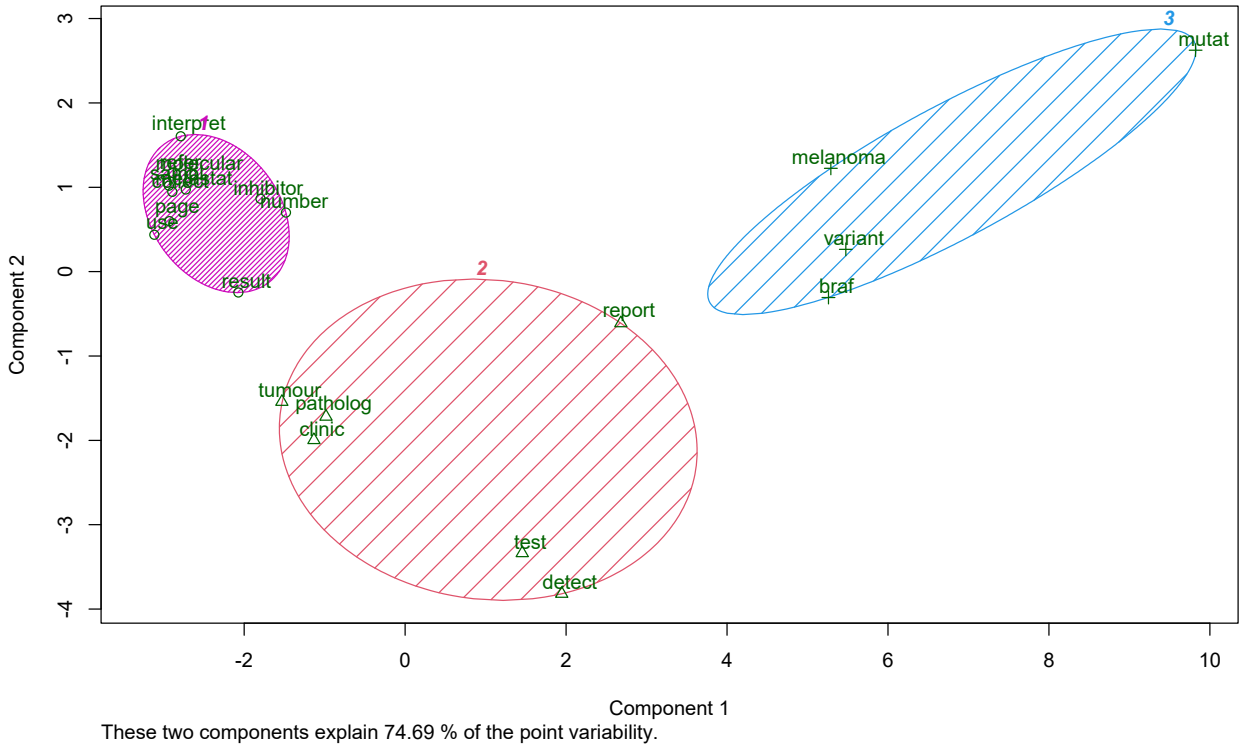
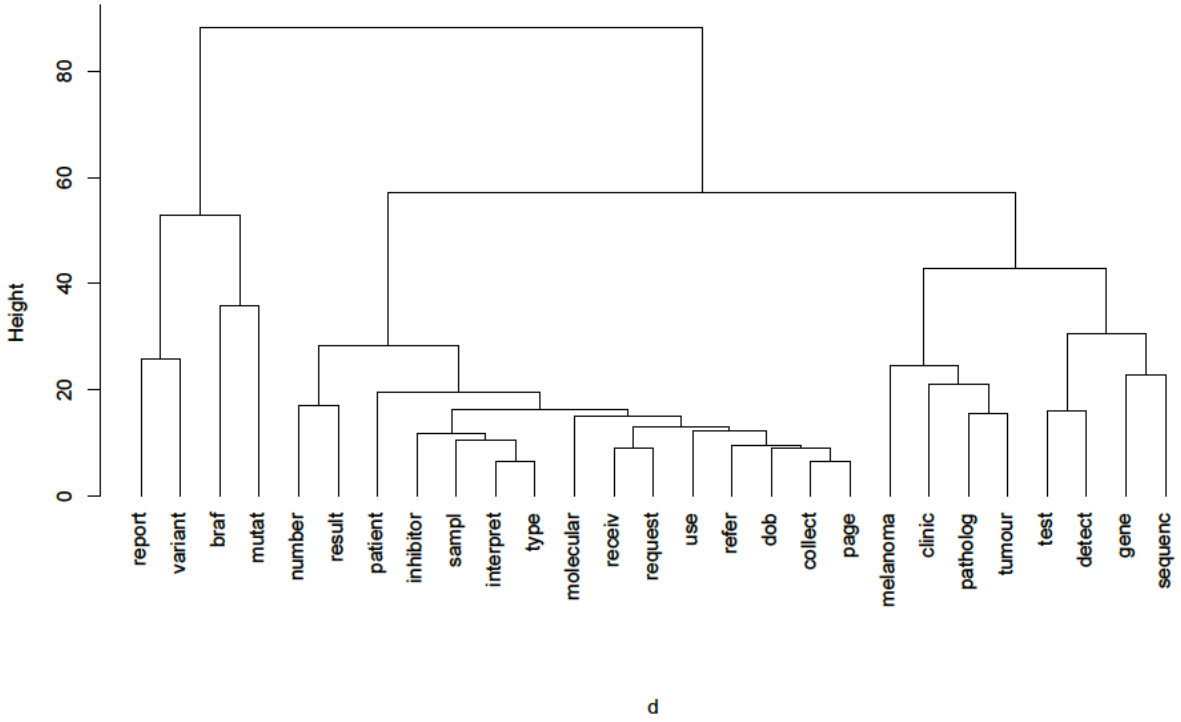


These two components explain 75.39 % of the point variability.



These two components explain 74.69 % of the point variability.

Group B: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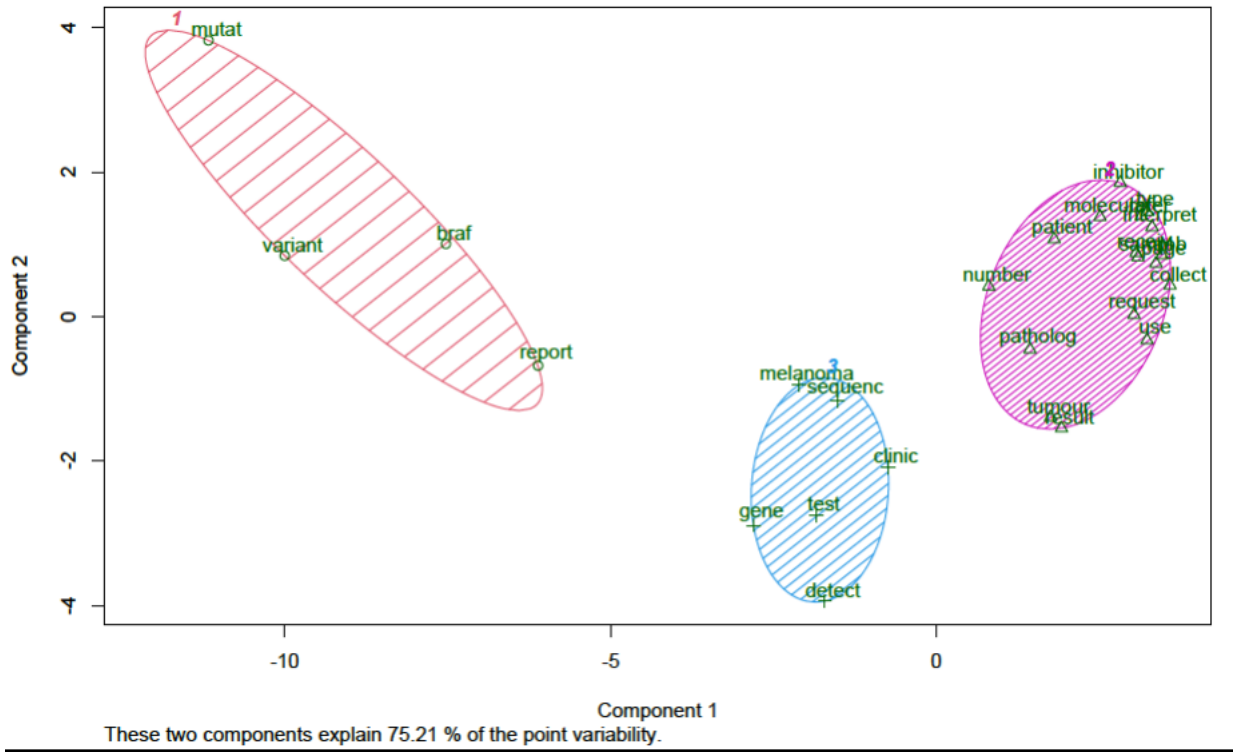
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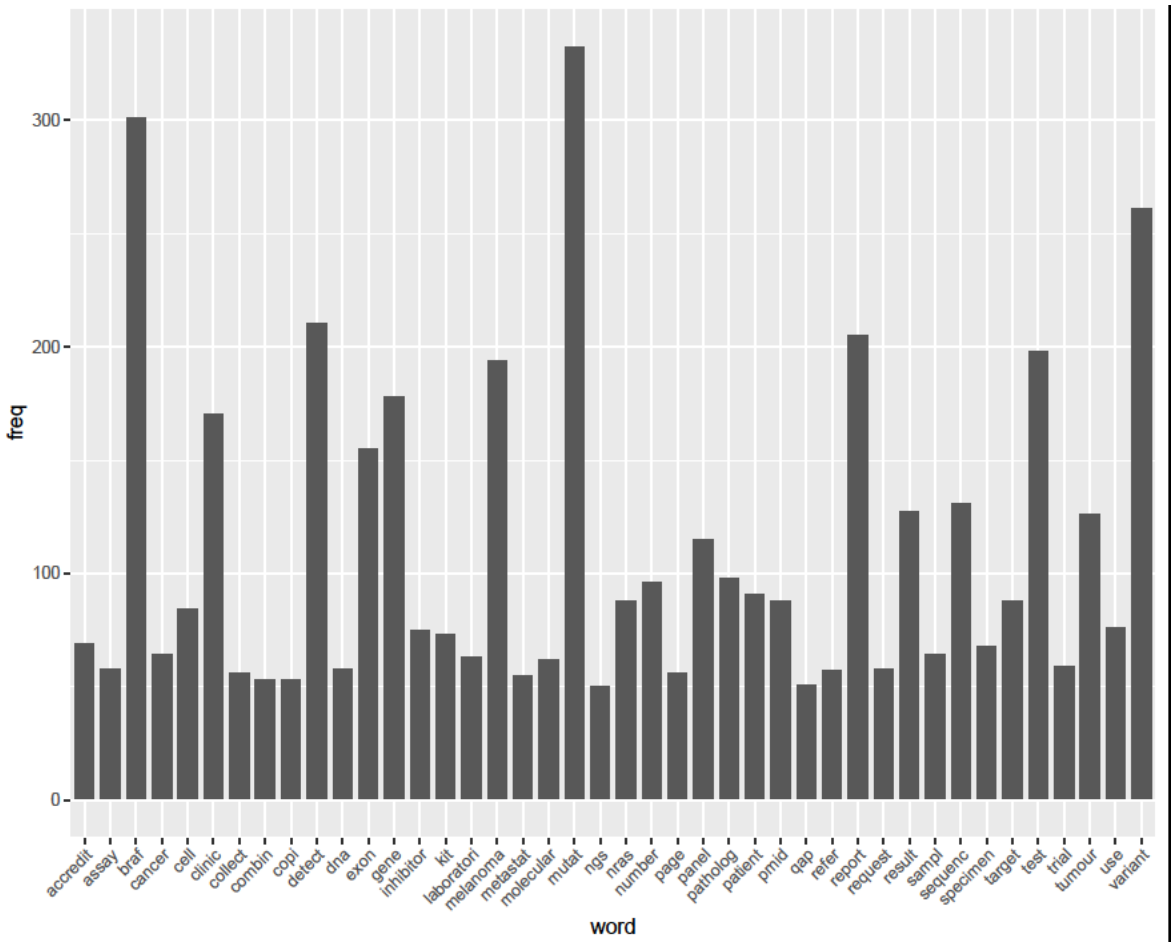
These two components explain 75.21 % of the point variability.

Group C: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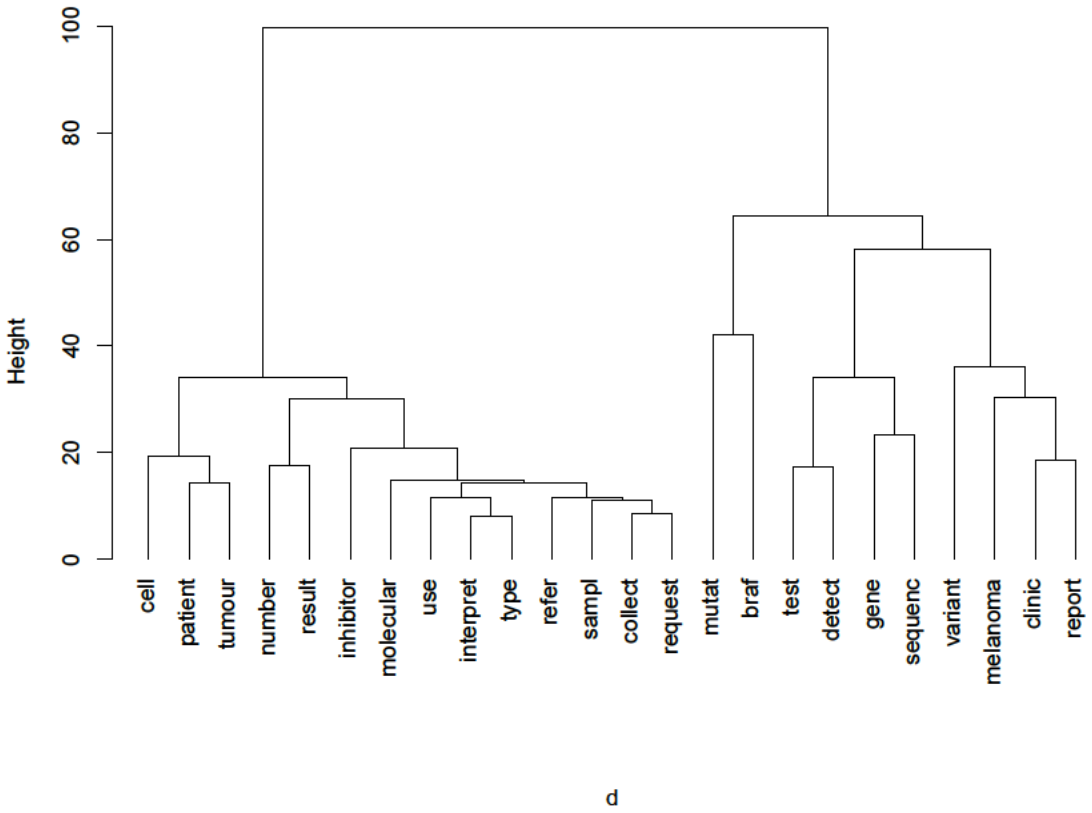
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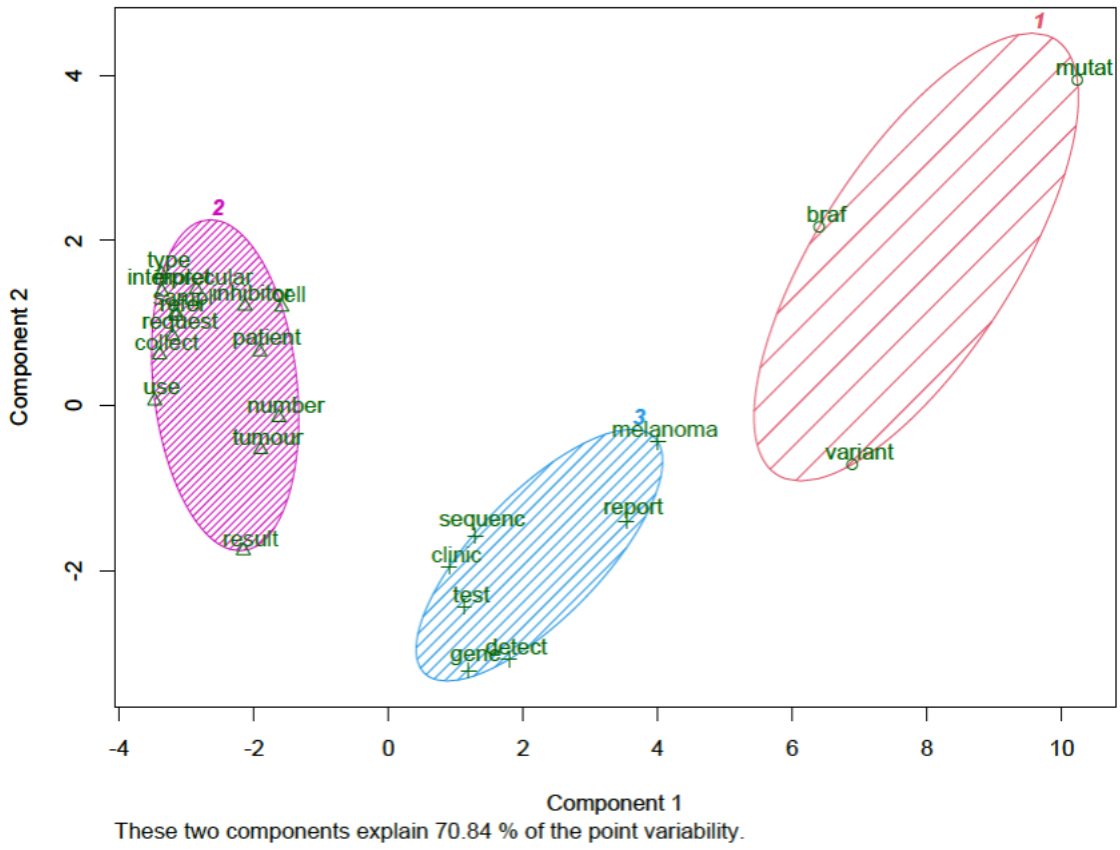

These two components explain 70.84 % of the point variability.