



# Navigating ethical challenges of integrating genomic medicine into clinical practice: Maximising beneficence in precision oncology

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The development of gene expression profiling and next-generation sequencing technologies has steered oncogenomics to the forefront of precision medicine. This created a need for harmonious cooperation between clinicians and researchers to increase access to precision oncology, despite multiple implementation challenges being encountered. The aim is to apply personalised treatment strategies early in cancer management, targeting tumour subtypes and actionable gene variants within the individual's broader clinical risk profile and wellbeing. A knowledge-generating database linked to the South African Medical Research Council's Genomic Centre has been created for the application of personalised medicine, using an integrated service and research approach. Insights gained from patient experiences related to tumour heterogeneity, access to targeted therapies and incidental findings of pathogenic germline variants in tumour DNA, provided practice-changing evidence for the implementation of a cost-minimisation pathology-supported genetic testing strategy. Integrating clinical care with genomic research through data sharing advances personalised medicine and maximises precision oncology benefits.

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The era of genomic medicine has witnessed major developments over the last decade, especially in the field of cancer genetics.<sup>[1]</sup> With the implementation of a new precision oncology scale for clinical actionability of molecular targets as proposed by the European Society of Medical Oncology in 2018, the utilisation of next-generation sequencing (NGS) technologies has become an integral part of cancer risk management.<sup>[2]</sup> The clinical utility of therapy targeted to genomic alterations stretches beyond immunohistochemistry (IHC)-based personalised medicine,<sup>[3]</sup> as demonstrated by significantly improved survival outcomes.<sup>[2]</sup> Although all malignancies are currently treated according to tumour type and/or stage, the gene expression information obtained from IHC can be enriched by NGS to increase the precision of the therapeutic approach. The genetic basis for differences in patients' response to therapy involves diverse signalling pathways, deficiency in the DNA double-strand break repair pathway, microsatellite instability and hypermutated tumour status.<sup>[4]</sup> Maximising beneficence in this context is challenging as every situation is unique.<sup>[5,6]</sup>

The use of molecular markers specific to each patient's cancer raised the expectation that targeted therapies could be administered independent of the underlying tumour histology.<sup>[7]</sup> However, the effectiveness of novel cancer-agnostic therapies is influenced by

tumour heterogeneity and time-dependent molecular evolution, posing significant hurdles in the shift to genomically informed treatment.<sup>[8]</sup> While some cells respond to anti-cancer medication, others develop resistance and antagonistic effects fostering increased toxicity and tumour growth.<sup>[9]</sup> The interpretation of tumour-only NGS for the selection of targeted therapies is complicated by the presence of deleterious genetic variants in normal tissue and non-malignant conditions, adding to the liability risks for laboratories and healthcare practitioners.<sup>[10]</sup> New multi-cancer early detection blood tests that have entered the genomics landscape with the promise to improve the survival rate and reduce the costs associated with late-stage cancer treatments,<sup>[11]</sup> require real-world efficacy studies in relation to existing oncology practices.

The infrastructure and support systems required to bridge remaining clinical implementation gaps, address healthcare disparities and align incidental findings of germline pathogenic variants in tumour DNA with concurrent familial risk, are limited in Africa.<sup>[12,13]</sup> The lack of a healthcare model designed to characterise and gain a better understanding of these requirements resulted in the development of a pathology supported genetic testing (PSGT) platform,<sup>[14]</sup> enabling the application of personalised medicine through integrating service and

research (PM-ISR). This approach provides a means to balance societal interest in the advancement of generalised knowledge v. individual benefit. Okunola *et al.*<sup>[15]</sup> accomplished this goal by using the PSGT platform for the return of research results to eligible South African (SA) patients with breast cancer participating in a pharmacogenetics study. Data sharing across diverse healthcare domains provided the opportunity to bridge the disconnect between inherited breast cancer caused by pathogenic *BRCA1/2* variants and vitamin D- or aromatase inhibitor-related osteoporosis risk. In the past, analysis of SA patients for the two major cancer susceptibility genes, *BRCA1* and *BRCA2*, was focused on surgical decision-making and to inform cascade family screening.<sup>[16]</sup> Today, the detection of pathogenic variants in the same genes can also serve as therapeutic targets for a new class of drugs called Poly (ADP-ribose) polymerase (PARP) inhibitors.<sup>[17]</sup> The finding that both germline and somatic *BRCA1/2* variants respond similarly to PARP inhibitors ushered in a new era of personalised medicine where the boundaries between germline and tumour genetics became blurred. This introduced new ethical challenges such as the detection of variants of uncertain clinical significance (VUS) and associated complexities in communicating meaningful laboratory results.

Benevolence in biomedical ethics as the central theme of this paper, relates to the obligation of healthcare professionals to ensure actions that collectively translate into benefit for patients. During the development of the multi-pronged PSGT platform for PM-ISR alongside standard pathology, experiences and uncertainties expressed by patients regarding shared clinical decision-making were noted. Insights gained from this perspective called for careful consideration of ethical duties continuously shaped by the depth of scrutiny applied by service providers. Fig. 1 illustrates an early example of precision oncology applied in a patient with metastatic ovarian cancer, who inspired the Open Genome Project as an NGS report-generating interface for clinical decisions beyond a single research objective.<sup>[12]</sup> Many learning points have been derived from this initiative, confirming clinically relevant relationships between tumour biomarkers and treatment responses on a case by case basis, using NGS technology combined with IHC.<sup>[15,18]</sup> The favourable impact of pharmacogenomic-derived recommendations on cancer progression supports the return of research results to individual patients. To prevent therapeutic misconception, the service and research arms of PSGT are guided by valid informed consent after careful consideration of previous pathology test results to help inform the appropriateness of NGS and the use of targeted therapies. Therefore, it is crucial to define when and how genomic assays add value to standard pathology in an ongoing manner. In the present study, we provide an overview of PM-ISR applied towards bridging remaining knowledge gaps in molecular pathology. We address healthcare disparities involving access to genomic assays for the selection of targeted therapies and align service delivery with patient needs while striving to balance conflicting ethical principles relevant to precision oncology.

### Balancing conflicting ethical principles in precision oncology

Genomic research in clinical practice poses ethical challenges for the implementation of precision oncology, emphasising the need to balance benevolence, particularly the utility principle, with autonomy and privacy concerns. Gupta *et al.*<sup>[19]</sup> reviewed many concerns raised

when using oncogenic mutations for targeted therapy. Adapting study design given sample size limitations characteristic of personalised medicine approaches, including n-of-1 clinical trials and small cohort implementation studies, requires institutional approval to uphold societal values and justice with regulatory oversight. The interplay of these ethical principles and the extent to which results can be generalised for clinical application varies in different situations, urging a reflective consideration of potential controversies in cooperative clinical decision-making. This is of particular relevance when one ethics principle conflicts with another. In an example presented by Munyaradzi,<sup>[5]</sup> it was stated that benevolence might be prioritised over autonomy if the latter impedes the use of genomic data to increase access to personalised healthcare. Utility as a principle of benevolence in biomedical ethics requires health workers to carefully analyse, evaluate and promote actions that are likely to benefit patients and the public.

The intention to increase access to precision oncology was reflected in the early hypothesis by Grant *et al.*,<sup>[20]</sup> exploring where 'additional information provided by a genomic test could fit into the context of the current clinicopathological prognostication of early-stage breast carcinoma'. Over the last decade, this research question has been answered by practice-changing evidence,<sup>[21,22]</sup> with the use of the dynamic PSGT research translation service.<sup>[14,23]</sup> While it was challenging to balance benefits to patients with conflicts of interest arising during the first health technology assessment (HTA) performed in 2009 by a SA medical insurer, the PM-ISR model developed because of this process opened new avenues for research focused on minimisation of healthcare costs.<sup>[24,25]</sup> Ethical analysis of PSGT by institutional review boards furthermore set new standards to protect patients and benefit the public, as evidenced by a transition from population risk stratification to personal utility in translational research projects.<sup>[15,26]</sup> This relates to the readiness checklist compiled by Jongeneel *et al.*<sup>[12]</sup> for the implementation of genomic medicine in Africa. Inter-university cooperation of professionals from different spheres of healthcare facilitates compliance with ethical and legal requirements as a critical step in translating advances in precision oncology into benefits for cancer patients.<sup>[27,28]</sup> Fear of invasive surgery and chemotherapy was found to be an important reason for delaying a cancer diagnosis, affecting the usefulness of genetic information in precision oncology.

A summary of pertinent ethical challenges being encountered in the application of precision oncology is provided in Table 1. With the increased merging of traditional boundaries between diagnosis and treatment in cancer management, a shared duty is assumed by members of the multi-disciplinary service delivery team. Defining authorisation levels aligned with interdependent roles in scientist training and clinician education programmes is crucial in achieving a shared goal and compliance with regulatory requirements.

### Bridging knowledge gaps in molecular pathology applied in oncology practice

Despite the potential of multi-omics to identify targeted therapies, some patients may benefit more than others due to distinct genetic and molecular profiles within a single tumour.<sup>[29]</sup> This heterogeneity has increased the ethical and legal challenges characteristic of interdisciplinary research that cuts across different healthcare domains. Medical scientists and clinicians share the responsibility for the introduction of clinically relevant genome-scale and targeted multi-gene NGS panels into the

**Table 1. Ethical issues encountered in the application of precision oncology and action points defined to prevent or address associated clinical dilemmas**

Ethical issues	Aspects to consider	Action points
Research ethics approval	Scrutinise the ethical conduct of translational research, including potential conflicts of interest that may be exemplified by the need for data sharing with provision of patient reports.	Transparently communicate the design and performance of processes developed to increase access to advanced technologies by generating data that informs continual improvement of genomic innovations and their applications.
Informed consent	Ensure that informed consent adequately covers issues, such as data sharing, secondary use of genetic information and the potential psychological impact of new knowledge to be communicated with the return of research results.	Provide clear explanations of the testing process and potential implications of the results to ensure that patients fully understand their rights and the potential for detection of variants of uncertain significance (VUSs) and incidental findings.
Data privacy and security	Protect patient genetic information by enforcing the Code of Conduct for the Insurance Industry that has been evaluated in relation to several genetic tests that were available in SA in 2004, partly reviewed in 2013. <sup>[14]</sup>	Evaluate how patient data is handled, stored and shared to prevent potential misuse of sensitive information that may lead to genetic discrimination given the scale of NGS implemented in SA over the last decade, both in the clinical and research environments.
Equity and access	Facilitate equal access to genomically informed clinical decision-making, irrespective of socioeconomic status, geographical location and disparities in healthcare infrastructure.	Identify and address potential biases in the development of genomic technologies that may lead to unequal health outcomes and ensure equitable access to targeted therapies.
Quality assurance and clinical validation	Utilise biomarkers and genetic information in treatment decisions based on robust scientific evidence to avoid premature implementation of unproven technologies as stand-alone assays	Implement new genomic assays in parallel with standard pathology for quality assurance to obtain clinically meaningful and reliable information by comparison, to support or avoid generalisation across clinical domains.
Communication and education	Foster effective communication between healthcare providers, clinicians, patients, researchers and medical schemes to facilitate characterisation and understanding of the complexities involved.	Reduce the potential for misunderstandings and unrealistic patient expectations through genetic counselling and feedback reports containing collective knowledge to enhance patient understanding and increase community engagement.
Patient advocacy and palliative care	Balance the need for aggressive treatment with quality of life after careful consideration of costly testing in patients with advanced disease who are unlikely to respond to targeted therapies.	Play an active role in advocating for patients, to help ensure that their rights and interests are considered in developing and implementing precision oncology programs early in cancer management.
Regulatory oversight and compliance	Administer targeted therapies based on genomic testing performed in compliance with the POPIA, while considering whether regulations adequately address emerging ethical challenges associated with this rapidly evolving field of healthcare.	Comply with regulatory requirements governing genomic testing by studying the requirements for adherence to standards set by governmental bodies as an integral part of the ethical conduct involving data management and reporting of results in patient reports and supporting scientific publications.
Longitudinal monitoring and information sharing	Develop strategies for long-term monitoring of treated patients to assess the potential for late-onset adverse effects or unexpected clinical outcomes, ensuring that advancements in personalised cancer treatment focus on patient well-being.	Leverage the interaction of healthcare professionals to help ensure that the ethical implications and challenges associated with genomic testing and administering of targeted therapies are well-understood and addressed in an interdisciplinary manner.
Cost and affordability	Consider the economic implications for healthcare systems and work toward cost-minimisation healthcare strategies to make personalised medicine more affordable and accessible, thereby reducing the financial burden on patients.	Integrate genomics into the broader context of clinical care by supporting the use of genetic testing when a less expensive pathology test would be insufficient to identify targeted therapies based on a comprehensive understanding of both genomic and pathological data.

\*POPIA = Protection of Personal Information Act [<https://www.assaf.org.za/wp-content/uploads/2023/04/ASSAF-POPIA-Code-of-Conduct-for-Research.pdf>]

healthcare system, with the aim to transform standard cancer care into precision oncology. PM-ISR aims to accomplish this goal by turning challenges into opportunities for the implementation of innovations in clinical practice, in line with the approach used by the Implementing GeNomics In pracTiCE (IGNITE) network.<sup>[30]</sup>

An important research question discussed earlier is whether NGS can be applied independently from standard pathology tests such as IHC. Conversely, IHC assessments of oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2) and

the proliferation marker (Ki67) status, can only approximate the Luminal A, Luminal B, HER2-enriched and basal breast cancer intrinsic subtypes.<sup>[31]</sup> Studies conducted in SA support the use of IHC in combination with the transcriptional profiling of 150 genes (MammaPrint/Blueprint®) to accurately classify patients with hormone receptor-positive early-stage (1 and 2) invasive breast carcinoma, with up to three positive lymph nodes, into different treatment groups.<sup>[22,32]</sup> Despite the highest level 1A evidence for accurate prognosis and prediction of chemotherapy benefit (yes/no) based on the 70-gene MammaPrint® test used in SA

from 2006, and implementation of OncoDEEP® in 2014 for advanced solid tumours as applied in Fig. 1 and to predict response to immunotherapy, these assays are only available within the private healthcare sector of SA. These genomics access disparities relate to the two-tier healthcare system in SA, affecting not only the optimal use of anti-HER2 targeted therapy, endocrine and chemotherapy but also the potential to prevent a second primary cancer in patients with hormone receptor-positive *BRCA1/2*-associated breast cancer.<sup>[21,22,24]</sup> Further motivated by the high false-negative rate of HER2 status described earlier by Dabbs *et al.*<sup>[33]</sup> performed as part of a 21-gene quantitative reverse transcription polymerase chain reaction (RT-PCR) assay (Oncotype DX®) in comparison with standard IHC and fluorescence *in situ* hybridisation (FISH), a research waiver of informed consent was granted for a quality assurance audit in SA.<sup>[20-22]</sup> This was in line with the SA Protection of Personal Information Act (POPIA), as specimens undergoing standard IHC and FISH testing were used in comparative microarray analysis for the same purpose. Reflex testing of tumours with discrepant IHC results,<sup>[21,22]</sup> provided an excellent example of turning challenges associated with tumour heterogeneity into opportunities, as pathology laboratories in SA started to add

the HER2 copy number together with the ratio determined by FISH in their laboratory reports from around 2014.<sup>[32]</sup> As Oncotype DX® was designed to guide chemotherapy decision-making and not anti-HER2 therapy, ongoing comparative studies as reported by Bai *et al.*,<sup>[34]</sup> remain important with the recent transfer of the 150-gene RNA-based microarray to the MammaPrint/Blueprint® NGS test kit to increase access.

### Addressing disparities in access to genomic assays for the selection of targeted therapies

Ethics guidelines generally reflect a limited focus on ways to increase access to targeted therapies, such as Herceptin (Trastuzumab) and PARP inhibitors in Africa, with oncology clinical trials including genomic tests perceived as complex and requiring expensive technologies. Maketha *et al.*<sup>[35]</sup> raised distributive justice concerns regarding *BRCA1/2* founder/recurrent variant testing in SA, stemming from the historical interpretation of associated ancestral lineages as markers of race or ethnicity, leading to the direction of cost-effective genetic testing to specific population groups that benefited more than others. This aspect was addressed in the design of the rapid BRCA point-of-care (POC) Research Assay evaluated by

Mampunye *et al.*,<sup>[24]</sup> which is applicable across the major ethnic groups in SA irrespective of age, family history or tumour type. The study cohort included a deceased patient diagnosed with invasive breast carcinoma of no special type, who tested positive for the pathogenic *BRCA2* c.7934delG variant in DNA extracted from her bladder tissue using tumour-NGS, 4 years after receiving a low-risk breast cancer recurrence score based on transcriptional gene profiling. The possibility of breast cancer metastasis due to the potential misclassification of the tumour's molecular subtype was ruled out by the histopathology report indicating a new primary cancer in the bladder, not breast cancer metastasis. Confirmation of *BRCA2* c.7934delG in the patient's germline DNA,<sup>[24]</sup> exposed a missed opportunity for the prevention of a second primary cancer caused by the most common *BRCA1/2* founder variant previously identified in the SA population.<sup>[26]</sup>

Although the above-mentioned patient did not fulfil the criteria for *BRCA1/2* testing at initial diagnosis of early breast cancer based on her age and family history, these genes were included upon the request of the treating oncologist when her tumour-NGS was performed as part of the OncoDEEP® precision oncology service. Effective communication between the clinician and laboratory scientists led to the integration of prior knowledge on the potential clinical implications for invasive urothelial carcinoma of the bladder,<sup>[36,37]</sup> into the dynamic PSGT process. Previously, only ovarian and triple-negative breast cancers were prioritised for tumour NGS including the *BRCA1/2* genes, but the detection of a SA founder variant supported the broadening of the laboratory protocol and reporting of *BRCA2* c.7934delG as an incidental finding in 2016. In this case, the identification of targeted therapies was the primary purpose of tumour-NGS and not to assess the patient's germline genetic status, as confirmed for *BRCA2* c.7934delG by Sanger sequencing performed in SA. By pinpointing this pathogenic *BRCA2* variant as a rare cause of metachronous breast and bladder cancer in the SA context, Mampunye *et al.*<sup>[24]</sup> initiated a process to intentionally report pathogenic *BRCA*/other germline variants in tumour DNA as secondary rather than incidental findings. This vision for the future of translational pharmacogenomics implies that any patient eligible for tumour

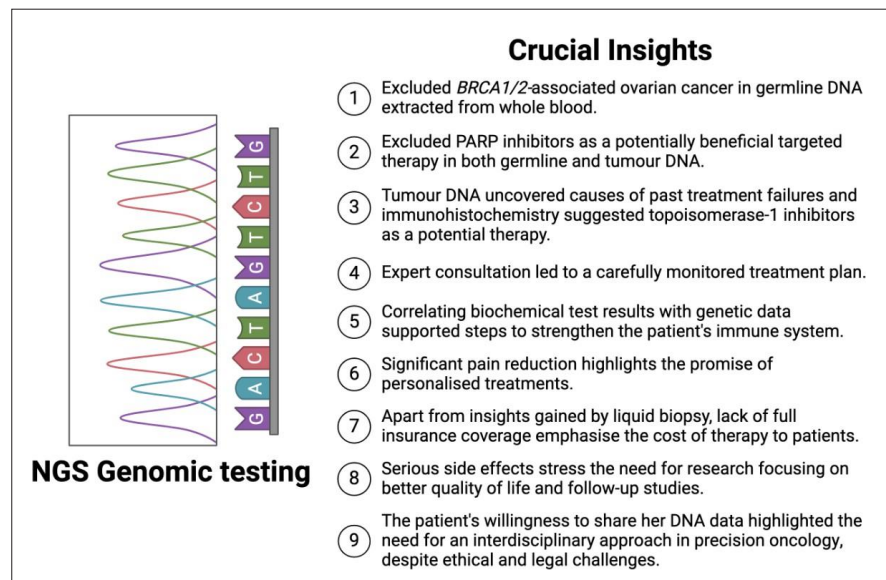


Fig. 1. Case presentation. Insights gained from using next-generation sequencing (NGS) to exclude or identify known genetic drivers of ovarian cancer (1-3), improve clinical outcomes through pathology-supported genetic testing and targeted treatment (4-6), and open new avenues for research by using the beneficence principle in aligning clinical service delivery with patient needs guided from her unique germline and tumour genetics profile (7-9). Image created with BioRender ([https:// biorender. com/](https://biorender.com/)) as summarised for this case from <https://cansa.org.za/cancer-genetics-how-one-patients-story-can-improve-the-lives-of-many>.

genomic testing and their at-risk family members could benefit from rapid germline testing for confirmation of the common SA *BRCA1/2* founder variants covered in the BRCA POC assay. A potential clinical dilemma caused by incidental findings can therefore be turned around to also benefit other breast cancer patients in future. For example, patients with early-stage Luminal A breast cancer may avoid chemotherapy despite the detection of a pathogenic *BRCA1/2* variant in germline DNA. This finding relates to the design of the 150-gene microarray/NGS assay that includes all 10 cancer hallmarks,<sup>[38]</sup> in contrast to the less comprehensive 21-gene RT-PCR assay found to be inaccurate in patients of African descent with hormone-dependent breast cancer.<sup>[39]</sup> The significant racial/ethnic disparity in survival shown for all three Oncotype DX® breast cancer recurrence risk groups (low, intermediate and high), highlighted the need for recalibration of these scores. However, if we hope to move away from using race as a proxy for the root cause of cancer development or recurrence, given the availability of other similarly priced precision oncology solutions designed for the same purpose, providing different scores by race would be a step backward.

In a survey performed among members of the Southern African Society for Human Genetics (SASHG), most respondents agreed that geneticists and clinicians should refrain from using labels such as 'black' or 'white' as far as possible since these phenotypic descriptors do not reflect the complexity of populations from the African continent.<sup>[40]</sup> This survey was prompted by continued controversy highlighted at the 'Moving beyond race' panel discussion at the 2019 SASHG conference. The congress organising committee, after reviewing the submitted congress abstracts and discussion with bioethicists, allowed potential presenters to reconsider whether their usage of race, ethnicity or population group labels was specifically relevant to the respective studies and whether any population group has been unfairly excluded or targeted. Positive outcomes included revision and retraction of offending abstracts as received from different geographic regions in SA, indicating that the issue identified was not localised to a single area or institution. It marked a significant milestone in transitioning away from racial to clinicopathological interpretations, strengthening the respect for persons in low to middle-income countries who are often denied access to clinical trials due to cost and other disparities.<sup>[41]</sup>

With the successful implementation of NGS using the OncoPrint™ BRCA Expanded Research Assay validated by the National Health Laboratory Service laboratory (NHLS) for routine use,<sup>[26]</sup> cancer patients are served in a manner that reflects the diverse SA demographics and population structure. Genetic testing in the public sector is funded by the Department of Health, with the patient being accountable for only a small fraction of the costs, if any. The currently used multigene NGS panel revealed a mutation-positive rate of approximately 15% in the patients studied, of which 25% are pathogenic founder/recurrent variants covered in the BRCA POC assay. To increase equitable access to targeted therapy in future amid ever-evolving NGS technologies,<sup>[26]</sup> *BRCA1/2* POC testing combined with genomic counselling may provide the optimal starting point for breast, ovarian, prostate and pancreas cancer patients who are all eligible for PARP inhibitors.<sup>[17]</sup> Although the benefits outweigh the risks, targeting the repair of damaged DNA may cause serious side effects in some patients, ranging from temporary tiredness and breathlessness due to alterations in the number of blood cells to an increased risk of infection and bleeding problems that need to be managed as part of cancer care.

## Aligning service delivery with patient needs through data sharing

Several tumour-based NGS applications have become commercially available in SA over the last decade including OncoDEEP® which currently targets more than 600 genes combined with IHC and other advanced technologies for shared decision-making. The use of this approach described by Laes *et al.*<sup>[42]</sup> identified the *KRAS* (c.35 G>A, p.G12D, rs121913529) variant in the ovarian cancer patient (Fig. 1). Although no targeted therapy was available for any *KRAS*-associated cancer type at the time of testing, the Food and Drug Administration granted accelerated approval to Sotorasib (Lumakras™, Amgen Inc., USA) for patients with non-small cell lung cancer, in May 2021. Apart from the potential unavailability of targeted therapy informed by NGS, variants can be missed if the gene regions spanning genetic alterations of interest are not included in the platform at the time of the analysis. This was demonstrated in a comparative study of two different diagnostic NGS platforms, with a discrepancy noted for *KRAS* and *ERBB2*.<sup>[43]</sup> The divergent results also raised the question of whether gene variants identified in tumour DNA, in the absence of confirmed protein expression of the relevant biomarkers, might be misleading. Stage 4 solid tumours with progression on at least one line of standard therapy or when there is no standard of care for the type of cancer diagnosed, were considered the most appropriate criteria for tumour NGS.<sup>[43]</sup> However, failing to act within a specific turn-around time referred to as the 'window of opportunity' may result in a waste of resources.

In SA, delays in the utilisation of germline or tumour NGS and treatment initiation based on the results cause much distress in families. Disappointment expressed by patients due to 'not knowing' earlier (at first diagnosis of cancer) about a precision oncology option is difficult to manage. This problem recently escalated to the extent that two different NGS tests have been requested from different service providers in SA, nearly 3 years after the original diagnosis of metastatic colorectal cancer. When this delay was questioned by the patient, the 'cost of the test and likelihood of a non-treatable result they may not want' were given as reasons. This was upsetting to the patient as the cost of NGS combined with IHC was considered minimal compared with the medical aid co-payments made for failed non-targeted therapies. Expert opinion furthermore differed regarding the feasibility of obtaining a new biopsy from the metastatic tumour for NGS instead of using the stored primary tumour collected at first diagnosis and when the results became available consensus could not be reached regarding the optimal treatment plan. This scenario represents a lost opportunity for shared decision-making, despite access to both NGS reports with a minor discrepancy (possibly due to tumour heterogeneity) that did not affect the patient's treatment. By equipping oncologists with expert-led knowledge derived from NGS combined with IHC, well-informed clinical decisions can be made with greater confidence.<sup>[18]</sup>

Current advances in molecular pathology, especially for risk management of non-communicable diseases (NCDs) such as breast cancer with a high incidence worldwide, need to be leveraged to address concerns of late diagnosis at advanced stages (3 and 4) in Africa.<sup>[44-46]</sup> This may partly be explained by transport problems, poor healthcare literacy, fear of missing work due to appointments and fear of invasive surgery and chemotherapy side effects. However, increased awareness about the availability of clinically validated

genomic assays where the costs are covered by medical schemes and/or state hospitals may increase the identification of early-stage breast cancer, enabling less invasive surgery and safe avoidance of chemotherapy in more patients.<sup>[28]</sup> Failure to inform patients about these genomic solutions based on the assumption that they will be unaffordable is considered unethical and legally unjustified, as a referral for a genetic/genomic test has implications for other family members who may pool resources to cover the cost.

Accurate estimation of cancer risk in families of deceased patients with deleterious variants in high-risk genes such as *BRCA1/2* and *TP53* known to contribute causally to tumour type, may benefit from stored germline DNA for follow-up testing in at-risk family members. To allow extended genetic testing of DNA from deceased cancer patients to the benefit of the extended family, Moremi *et al.*<sup>[47]</sup> applied PM-ISR for the integration of germline and tumour genetics across the illness and wellness domains. Evaluation of a multiplex NCD-pharmacogenetics assay in postmenopausal women with hormone receptor-positive breast cancer previously assessed for vitamin D and homocysteine levels as part of a biochemistry test panel,<sup>[15]</sup> provided supporting evidence to position POC genomics at the interface of familial, lifestyle and therapy-induced risk assessment in future.<sup>[48]</sup> Although screening for genetic underpinnings of lifestyle- or treatment-related comorbidities is not the primary target for genomic testing in cancer patients, secondary findings change how each individual is supported in their efforts to live healthier after diagnosis and treatment. Longitudinal research provides a comprehensive perspective on the trends, causal relationships and the impact of both external and intrinsic factors on the evolution of cancer genomics and DNA methylation over an extended timeframe. As traditional research ethics principles aimed at the protection of individual study participants are evolving towards serving the interests of society at large, Vos *et al.*<sup>[49]</sup> provided a compelling argument for a collaborative approach towards collective knowledge application.

Efficient collaboration between healthcare practitioners and laboratory scientists is imperative to enhance clinical access in the realm of precision oncology, notwithstanding the numerous challenges that may arise during its implementation. Fig. 2 shows the proposed NGS workflow for PM-ISR, from obtaining



Fig. 2. A decision-making framework for navigating ethical challenges anticipated during the implementation of next-generation sequencing (NGS) extending from first tier point-of-care (POC) genotyping to genome sequencing using the pathology-supported genetic testing (PSGT) strategy for integration of service and research. Genetic counselling support is provided through-out the process involving 1) the use of research translation tools requiring technical capabilities to increase access to precision oncology with clinical oversight; 2) consideration of different perspectives and accepting shared responsibility for addressing potential ethical issues that may arise during the laboratory implementation phase; and 3) decision-making based on patient preferences and reflecting on the outcome of genetic/genomic testing service delivery in parallel to the generation of a research database to support best practice in personalised medicine [<https://www.icpermed.eu/en/798.php>].

informed consent for first tier genotyping elevated to multi-gene panel testing and whole exome/genome sequencing in uninformative cases. Challenges encountered during the integration of research and service delivery are addressed by appropriate test selection aided by genetic counselling to facilitate clinical decision-support, elevation to extended genetic testing in uninformative cases and clinical implementation of risk reduction strategies tailored to the needs of the individual.<sup>[15]</sup> An umbrella informed consent document, refined over more than a decade, is completed together with a structured report-generating questionnaire to help clarify the benefits and limitations of PSGT as a novel approach to integrating clinical service delivery with translational

genomic research. Moving from paper-based to electronic informed consent for genetic testing of NCDs was justified by the emergence of the coronavirus disease in 2019,<sup>[50]</sup> to enable a phased research translation process encouraging freedom to consent or decline testing without coercion. Understanding the risks of participation in translational research that may incorporate aspects of infectious diseases' host genetics, thus represents the first step in collecting personal information for the generation of adaptable feedback reports in the form of a case presentation for each patient, reflecting the collective knowledge of the researchers and healthcare practitioners involved in the research translation process. This is the purpose of the PSGT strategy: shifting the focus from volume of services to

quality of care that prioritises early interventions and enhancement of individual patient experiences.<sup>[51-53]</sup>

## Conclusion

The development of a framework for ethical decision-making started with the identification of important issues to address in precision oncology, followed by fact-finding as undertaken by the Cancer Association of SA for the MammaPrint® service.<sup>[54]</sup> This provided the first example of maximising beneficence in precision oncology in SA, based on solid scientific evidence from locally generated tumour genomics data incorporated into a new care pathway. PM-ISR enabled clinical, scientific, ethical and legal challenges encountered in pursuing precision oncology to be addressed as a shared responsibility at the intersection of participating laboratories and clinical practice. PSGT incorporating rapid POC testing for utilisation in remote areas to promote inclusivity of precision medicine will be a vital step towards achieving equitable cancer care in SA. This requires the development of a practical quality control plan incorporating patient-reported outcomes to determine the long-term impact of precision oncology treatments.

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