Challenges in integrating molecular profiles into clinical cancer care

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Summary Profiling of malignancies with next-generation sequencing (NGS) is now routine in clinical practice. While many cases of approved targeted therapies are straightforward based on well-characterized alterations, applying large NGS multigene panels to therapeutic use is frequently challenging. In this article, variant interpretation, therapy matching, and final treatment selection challenges are discussed.

Keywords Next-generation sequencing application · Variant annotation · Therapy matching · Challenges · Clinical tiering

Background Targeted therapies are now standard in solid and hematological malignancies. Their regulatory approved use is either mandated by the clinical setting or is based on the presence or absence (resistance markers) of defined biological alterations. Initially, well-characterized hotspot mutations (e.g., KRAS) were analyzed, known to oncologists and pathologists alike. Complexity increased with tumor suppressor genes such as BRCA1/2. Still, a limited number of actionable genes, mostly recurrent oncogene hotspots, and generally a single actionable alteration per patient rendered clinical application of sequencing results comparatively straightforward. Affordable multigene analysis through next-generation sequencing (NGS) and an ever-increasing number of actionable alterations have profoundly changed the situation. Where before the technical aspects of sequencing were central, the focus has now shifted to challenges regarding the complexity of variant interpretation, successful therapy matching, and selection of the subsequent therapy regime. Our review aims to cover the main obstacles encountered in NGS starting from technically validated variant data (i.e., after excluding technical sequence artifacts). In chronological order of the workflow, we address challenges in NGS variant annotation, variant ranking for expected clinical benefit, therapy matching, and reimbursement issues.

Challenge: Variant interpretation and clinical tiering

Correct variant annotation is the most critical step in deriving clinical benefit from genomic tumor profiling. The goal is to detect the tumor’s relevant driver mutation(s) and identify those that are druggable for therapy. Comparatively few—less than 10—such molecular drivers have been estimated to be responsible for tumor propagation in most tumors [1]. Their distinction from frequently numerous passenger mutations is essential. Incorrect variant annotation risks missing actionable alterations leading to possible undertreatment, while overinterpretation of passenger mutations may lead to overtreatment and treatment failure. Technically, NGS is used for comprehensive genomic profiling either within the pathology department or by an external, commercial provider. Variants are relayed to the clinician in one of several forms. Alterations are commonly reported directly after technical validation (e.g., BRAF V600E) for single genes and hotspot results. The clinician is then tasked to know the biological relevance (pathogenicity) and
the actionability/druggability of the alteration from seminal trials or the literature. Alterations are usually straightforward to interpret and represent companion diagnostics for standard therapies.

Alternatively, the pathologist provides a tiered assessment of the variants’ pathogenicity according to the nomenclature of criteria initially established for germline variant assessment [2] and subsequently also used for somatic variant interpretation [3, 4], e.g., five-tiered: pathogenic, likely pathogenic, unclassified variant, likely benign, or benign. Pathogenic and likely pathogenic alterations are deemed relevant for further evaluation of actionability by the clinician, and variants are assessed with or without a formal clinical tiering. Clinical tiers are most commonly assigned according to the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) [5] or the American Joint Consensus Recommendations (JCR) [6]. In the third setting, the molecular alterations are annotated only by their clinical tier. A lack of pathogenicity is expressed by assigning a low tier (JCR tier 3 and 4), and in ESCAT “tier X” or no tier assignment for unclassified variants.

Determining pathogenicity and clinical treatment options can be time-consuming and complex. While well-known variants can be directly queried from established germline or somatic databases (e.g., ClinVar, Catalogue of Somatic Mutations in Cancer (COSMIC)), novel or rarely detected alterations need de novo annotation in a multistep process. Currently, this process is insufficiently formalized and performed with a high degree of individualized expert opinion appraisal of preclinical and clinical data in conjunction with the molecular properties of the alteration in question. In addition, evidence of recurrent detections in malignancy, exclusion of known benign germline variants (polymorphisms), literature data, and computational predictions, among others, need to be taken into account. Only very recently were comprehensive and detailed proposals geared explicitly towards de novo variant interpretation of somatic variant pathogenicity formally proposed [3, 4], similar to the scoring system introduced by the American College of Medical Genetics (ACMG) for germline variant evaluation in 2015 [2]. These ACMG guidelines have standardized germline variant interpretation and have (at least partially) been already applied to somatic variant annotation [7, 8].

Somatic NGS data frequently yield more alteration calls than germline analyses, especially in genetically unstable tumors. Furthermore, increasingly comprehensive NGS analyses have led to considerable curation workload growth [9].

The labor-intensive manual in-depth analysis that can be performed for single variants in germline analysis are in practice not feasible for the high numbers of somatic variants often encountered in somatic tumor analysis when large multigene panels or even whole exome sequencing (WES)/whole genome sequencing (WGS) is performed. Still, timely and cost-effective annotation is mandated.

Indeed, turnaround time is a significant challenge in patients with sometimes rapidly deteriorating clinical performance levels. Proprietary and open source decision support tools have therefore filled this gap, such as Varsome® (Saphetor, Lausanne, Switzerland), Qiagen Clinical Insight (QCI) Interpret® (Qiagen, Hilden, Germany), Navify® Mutation Profiler (Roche, Basel, Switzerland), PierianDx® (Pierian, Creve Coeur, Missouri, USA), OpenCRAVAT [10], OncoKDM® (OncoDNA S.A., Gosselies, Belgium). Some offer automated de novo annotation according to ACMG criteria (e.g., [7, 8]). Combined with a synopsis of data from relevant databases and algorithms, they allow for annotating hundreds of alterations in-depth at the required turnaround times.

**Challenge: Clinical tiering**

The two most commonly used clinical tiering systems, the American JCR guidelines and the European ESCAT guidelines, albeit similar at first glance, differ fundamentally in their inclusion of clinical objectives (diagnostic, prognostic, and predictive evidence) [11]. Furthermore, the inclusion of evidence differs (US Food and Drug Administration approval information for JCR), as does the complexity of their application. Consequently, discordant clinical tiers are not infrequent [11], which is usually perceived as confusing and challenging [12]. In addition, the ESCAT guidelines necessitate the evaluation of the magnitude of clinical benefit score (MCBS) as defined by ESMO [13] in tier I target substratification. The ESMO-based service provides clinicians with readily accessible score cards for individual drugs supporting practical implementation. Yet, this approach fails to define the in-depth basis of specific mutation–drug matches in the context of a molecular tumor board [14].

MCBS scoring can be time-consuming depending on the gene and the clinical evidence to be assessed. Hence, a simplified assessment of the ESCAT guidelines omitting formal MCBS scoring but directly appraising progression and survival data of relevant clinical trials may well lead to equal clinical management and might be more time-efficient, easier to convey and to discuss.

The druggability of a gene is currently assumed to be similar across histological entities, provided (pre)clinical data to the contrary are absent. Overly simplistic, this might contribute to the only approximately 20% clinically meaningful response rates (as defined by a ratio of the progression free survival [PFS] of the last therapy line to the PFS of the previous therapy line [PFS2/PFS1 ratio] >1.3) of NGS profiled and treated patients beyond standard therapy [15]. Still in its early tracks, efforts such as within the ClinGen project [16] scope aim to curate driver
genes in a tumor entity-specific context. Prominent examples include the lack of benefit of single-agent BRAF inhibition in colon cancer [17] and ineffective PARP inhibition beyond entities associated with increased heritable cancer risk in BRCA1/2 [18].

The clinical tiers deemed suitable for treatment are context-dependent (academic vs. routine) and dependant on the payer's attitude toward cost coverage. Challenging NGS applications as discussed herein, imply comprehensive profiling and include therapy matching beyond approved standard therapies (i.e., beyond ESCAT tier I). In our opinion, the resources consumed for extended NGS profiling justify treatment recommendations based on targets from ESCAT tier I–IIIa (approved/high-level evidence targets repurposed across entities) for clinical routine. In contrast, targets of lower grade ESCAT tiers may be of interest to academic studies and eventually a therapy of last resort for progressed patients, but most payers/trusts will at present remain unconvinced to cover these costs.

Challenges beyond target detection: Timing, toxicity, drug availability, and costs

The timing of NGS profiling in later-stage disease is essential. Rapid performance deterioration and unacceptable toxicity that precludes therapy are among the main reasons for exclusion or clinically futile molecular diagnostics. Too late an inclusion rendered 44% of consented patients in the I-Predict trial unfit for therapy at the time of intended NGS profiling [19], and patients with <3 month life expectancy are not recommended to undergo NGS profiling [20]. Increasingly, multiple druggable targets can be identified in a tumor [15]. Unfortunately, the lack of appropriate toxicity data has become a bottleneck for combination therapy. Possible combinations of immune checkpoint inhibition or PARP inhibition plus kinase inhibition therapy are now not infrequently seen. The sheer number of possible drug combinations makes acquiring clinical data on specific toxicity difficult and may therefore necessitate prediction by IT algorithms or use of in vitro data as already attempted for estimating synergy of combinatorial therapies [21, 22].

Finally, obtaining cost coverage and drug availability is an essential barrier to therapy effectuation [23]. Naturally, payers and their assessing representatives find themselves at an information disadvantage concerning the complexity of NGS workup. In our experience, it is paramount to communicate as clearly and concisely as possible with the colleagues tasked with cost coverage approval. Standardized clinical tiering and assessment of expected clinical benefit (e.g., through ESMO's Magnitude of Clinical Benefit Score [MCBS]) may benefit this goal but would burden an already time-intensive process with additional costs and workload.

Conclusion

Further standardization and automatization of somatic variant annotation are necessary and must proactively be brought into the spotlight of the academic discussion. Furthermore, a more profound, tumor context-dependent, biological understanding of targets that can effectively be incorporated into the routine NGS workflow is needed to identify therapies of clinically meaningful response more accurately.

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Conflict of interest S.W. Jahn and P.J. Jost declare that they have no competing interests.

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