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PRECISION ONCOLOGY DECISION SUPPORT: CURRENT APPROACHES AND STRATEGIES FOR THE FUTURE

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Abstract

With the increasing availability of genomics, routine analysis of advanced cancers is now feasible. Treatment selection is frequently guided by the molecular characteristics of a patient's tumor, and an increasing number of trials are genomically-selected. Furthermore, multiple studies have demonstrated the benefit of therapies that are chosen based upon the molecular profile of a tumor. However, the rapid evolution of genomic testing platforms and emergence of new technologies makes interpreting molecular testing reports more challenging. More sophisticated precision oncology decision support services are essential. This review outlines existing tools available for health care providers and precision oncology teams, and highlights strategies for optimizing

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decision support. Specific attention is given to the assays currently available for molecular testing, as well as considerations for interpreting alteration information. This article also discusses strategies for identifying and matching patients to clinical trials, current challenges, and proposals for future development of precision oncology decision support.

Keywords

Precision Oncology Decision Support; Bioinformatics

INTRODUCTION

The use of targeted therapies in molecularly-selected patients has led to a paradigm change in cancer medicine. However, although close to 50 targeted therapies have been approved by the Food and Drug Administration (FDA) for solid tumors, only half of these targeted therapies have predictive biomarkers associated with their FDA approval (Table 1).

As the breadth of molecular testing and the number of biomarker-selected trials grow, clinicians are less able to rapidly interpret molecular reports during a clinical encounter and determine optimal approved or investigational therapies. The complexities of these processes are highlighted in Figure 1. A survey at a major cancer center demonstrated that many oncologists lack confidence regarding their ability to interpret genomic information(1). As a result, a new field of precision oncology decision support has emerged. The focus of this review is to provide novel insights into the current tools available for precision oncology decision support, as well as to help identify opportunities for future development.

MOLECULAR TESTING

Genomic Testing

Identifying clinically-relevant characteristics of an individual tumor is critical to precision oncology. Historically, oncologists have chosen therapies and determined prognoses based on site of origin and histology. In select tumor types, oncologists began incorporating biomarkers, such as immunohistochemistry for HER2 and estrogen/progesterone receptor status in breast cancer(2,3). Today, genomic characterization is increasingly being used to guide treatment decisions, especially in patients with advanced disease.

Genomic characterization has been performed using a variety of strategies that range from hotspot exon sequencing of a select panel of genes to whole genome sequencing(4–8). Early genomic evaluations focused primarily on single nucleotide variations (SNVs). Assessments have now expanded to evaluate for other alterations, including indels, translocations, and copy number variations. Although assays to detect these alterations are not as widely available as those for SNVs, several such alterations have been successfully targeted(9–12). Furthermore, some of these successes were for alterations present in rare tumor types that are unlikely to be studied in tumor-specific clinical trials, as in the case of *NTRK* fusions(12,13). This gave rise to the possibility of tumor-agnostic, molecularly-driven registration strategies.

Panel testing for genomic alterations is becoming more widespread. Many treating physicians utilize commercial testing through companies such as Foundation One (Foundation Medicine, 315 genes) or Caris Molecular Intelligence (Caris Life Sciences, 592 genes). Some institutions have implemented commercial platforms such as Ion Torrent AmpliSeq Cancer Hotspot Panels (ThermoFisher Scientific, 50 genes) or Oncomine Comprehensive Assay (ThermoFisher Scientific, 143 genes V1, 161 genes V3). A small number of institutions have developed their own platforms, such as the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT, 468 genes) assay(14,15). Although local testing requires local molecular diagnostic and bioinformatics support(14,16), it also allows for customization and inclusion of specific rarer alterations within a gene panel. As more actionable alterations are identified, having the ability to alter the available panels to meet local needs may be advantageous.

Whole exome sequencing (WES) is a technique that sequences all the protein-coding genes in a genome (known as exome). This can identify the genetic variants that alter protein sequences at a lower cost than whole genome sequencing (WGS) (the process of sequencing the complete genome). Whole exome and whole genome sequencing have predominantly been research tools, but more recently are being introduced to the clinic(17,18). These strategies have the disadvantage of needing a stronger bioinformatics and decision support pipeline and potentially providing greater information burden on the clinical providers. In contrast, while hot spot sequencing is much cheaper and easier to support from a bioinformatics perspective, these sequencing efforts do not provide as much opportunity for discovery. Panel testing of 100–500 cancer related genes appear to have the greatest utilization at this juncture. Panel tests have the advantages of needed relatively small amounts of DNA, ability to support some discovery, and providing enough coverage and sequencing depth to allow for detection of subclonal variants. WES may especially have a role in patients with no actionable alterations on panel testing, in rare tumors, or in tumors that infrequently have alterations on commonly tested genes. The utility of early routine WES versus selective WES testing is likely to become more apparent over the next few years.

Treating oncologists must be aware of the relevant actionable alterations in the diseases they treat (Table 2). Knowledge of the expected genomic landscape will allow oncologists to order genomic testing early in diseases that have many genomic drivers linked to approved therapies, such as in the case of NSCLC or melanoma(19). This understanding will also ensure that oncologists request assays that evaluate for alterations more frequently found in the patient’s tumor type (e.g., FGFR fusion testing for cholangiocarcinoma, TRK fusions in secretory breast cancer), especially when patients are interested in investigational therapies.

Tumors may show genomic evolution over time or may have intra- and intertumor heterogeneity between primary and metastatic sites(20,21); therefore, repeat tumor sampling is being pursued more frequently. Due to greater tissue availability, testing in patients with metastatic cancer is often done on primary tumors. Although one would expect most truncal alterations will be found in the primary tumor, when more than one tumor sample available, the most current sample should be used to account for genomic evolution. Although biopsies can usually be done relatively safely, issues surrounding patient inconvenience, procedure-

related pain and complications, and biopsy costs make proximal or serial tissue testing challenging. Insurance coverage and procedural availability may also vary greatly, making broad recommendations difficult to provide. Therefore, the role of repeat biopsies and sequencing remains controversial. Considerations while deciding between analyzing an archival sample and obtaining a new sample include time since sample collection, number of lines of treatment given in the interim, types of treatment lines, as well as logistical considerations including feasibility and safety of a new biopsy. Although there is significant concordance in specific mutations between primary tumors and metastasis, there may be changes in actionable alterations(21). There are also now many established mechanisms of acquired resistance to targeted therapies such as acquired mutations in *EGFR* and *ESR1* with EGFR inhibitors and endocrine therapy respectively, and *BRCA* mutation reversions with PARP inhibitors, demonstrating the value of repeat sampling and genomic analysis(22,23). For this reason, when possible, genomically-matched trial designs should incorporate “progression biopsies”: biopsy of a progressing lesion in patients who experience progression after initial response or prolonged stable disease. This can give important insights into mechanisms of acquired resistance and ways to overcome them early in drug development.

Liquid Biopsies

The advent of cell-free DNA and circulating tumor cell testing (i.e., “liquid biopsy”) has provided less invasive modalities for genomic testing. Liquid biopsies were initially undertaken using allele-specific polymerase chain reaction and flow cytometry(24). Now, next-generation sequencing panels are increasingly employed(25). The decision to use panel testing versus PCR-based testing depends on the underlying question. When a known mutation is being followed during treatment, it may be more cost effective and sensitive to perform focused testing. However, initial testing or subsequent treatment planning assessments may require a broader panel. Furthermore, serial sampling of plasma with broader sequencing may allow for the detection of acquired resistance mutations in the targeted gene, as shown with EGFR, FGFR and HER2 inhibitors(26–28). Larger panels can also facilitate identification of alternate resistance mechanisms.

Liquid biopsy also has several limitations. It may miss small amounts of mutant DNA, as in the cases of lower mutant allele frequency (subclonal) alterations, patients with limited disease burden, and tumor lineages that release small amounts of DNA into the circulation. It is a strength that liquid biopsy reflects the pool of alterations in a patient, but it may also be more difficult to assess mechanisms of resistance in patients with mixed response. Furthermore, certain alteration types may be more difficult to detect, such as copy number variations(29). With the exciting advances made possible by single cell techniques in the assessment of tumor heterogeneity and subclonal detection of alterations(30,31), it is likely that liquid biopsies will complement rather than replace tumor testing in the foreseeable future.

Multianalyte Testing

Although genomics has been the primary tool in precision oncology recently, there is growing recognition that only a subset of patients has truly compelling genomic alterations

and even then only a subset of patients responds to genotype-matched therapy. These is a clear need to move beyond genomics only, and explore the utility of multianalyte testing, independently or in conjunction with genomic testing.

As technology has evolved, the field has also begun incorporating transcriptomics and proteomics. Although microarrays have traditionally been used to evaluate transcriptomics, RNAseq in increasingly being used (6,8,32). RNAseq has already been used to help identify novel alteration types that would be missed at the genomics level, such as fusions and rearrangements(33,34). RNAseq also has the advantage of determining whether the genomic alterations are reflected at the RNA level (e.g., are the oncogenic mutations expressed and are the amplified genes overexpressed?). Newer technologies for proteomics including reverse-phase protein array, mass spectrometry, and cyclic immunofluorescence have great potential. High throughput proteomics techniques will likely provide further novel insights into potential targets and resistance mechanisms once these techniques are optimized for the clinical setting(35,36). Many of these novel characterization strategies will likely transition from the research environment to the clinical setting in the future. Successful clinical utilization of these rapidly evolving technologies requires a decision support framework to help interpret molecular results.

FUNCTIONAL ANNOTATION AND DECISION SUPPORT

Functional impact and therapeutic implications

As genomic testing platforms and both preclinical and clinical data expand, the interpretation of genomic reports becomes increasingly complex. Annotation of molecular alterations is the process of detailing what change has occurred, and the clinical significance of that change. A change in an amino acid can lead to a change in the activity, expression, or stability of the expressed protein, or to no change. Even within the same gene, one alteration might confer sensitivity to treatment, while another may result in resistance (e.g., *EGFR* mutations and EGFR inhibitors(26,37)). Thus, the functional significance of each alteration must be assessed for clinical decision making. In spite of our growing genomic knowledge, larger panels or whole exome sequencing often reveal variants of unknown significance (VUS), in addition to variants that are well-characterized (such as BRAF V600E). The functional impact of these VUSs is simply not yet known.

There are multiple computational algorithms designed to predict the functional impact of specific aberrations, however, their predictive ability remains limited(38). There is growing interest in functional genomics: generating specific mutations and assessing the effect of introducing these mutations into reporter cells, as well as assaying the effect of introducing the mutant gene versus wildtype gene on cell growth and survival and on pathway activation. However, it remains unclear if these *in vitro* assays will be uniformly effective in classifying the functional impact of alterations.

A consensus about how to classify therapeutic implications is also lacking. The use of predetermined levels of evidence may aid in data interpretation, but no universally agreed-upon system currently exists(39–41). Recently, the Association for Molecular Pathology, the American Society of Clinical Oncology, and the College of American Pathologists have

released a consensus statement. They propose a four-tiered system for clinical significance of somatic sequence variations, ranging from variants with strong clinical significance to variants that are benign or likely benign(42). In practice, however, there are still inconsistencies in terms of predicting therapeutic implications(8,16,39,43–48). Thus, clinical judgment is still required in addition to integration of data from large databases and literature reviews.

Actionability of genomic alterations

"Actionability" of an alteration has been broadly defined to mean having potential clinical utility(8,16,39,43–48). A somatic aberration may be actionable if it alters prognosis or predicts therapy sensitivity/resistance. In some scenarios, prognostic markers may help guide therapeutic choices (e.g., *TP53* mutations confer worse prognosis in leukemia and may lead to consideration of transplantation). Germline alterations may also be actionable by increasing the risk of cancer or other hereditary diseases, predicting therapeutic response, or altering drug metabolism and thereby affecting drug efficacy or toxicity. Overall, actionability implies that knowledge of that specific alteration's presence would change patient management.

In precision oncology, much of the emphasis has been on determining therapeutic actionability. The definitions used at MD Anderson Cancer Center's Precision Oncology Program are outlined in Supplemental Table 1. However, there remains no consensus on when a genomic alteration should be acted upon. Limiting actionability to FDA-approved therapies for a specific biomarker is restrictive, and fails to allow for use of genomic information to inform enrollment onto clinical trials or for predicting risk. Alternatively, treating patients with suspected benign alterations or variants of unknown significance with genomically-targeted agents would decrease the likelihood of achieving clinical benefit in patients. It would result in patients receiving potentially toxic and costly futile therapy that delays initiation of effective therapeutic options, and would dilute potential efficacy seen in trials. As the field continues to evolve, our understanding of which alterations are actionable will also grow, and selected VUSs will be reclassified as their function and therapeutic impact is understood. We will need to be able to quickly adapt to emerging information.

Use of Available Resources

Most decision support teams report using PubMed or other search engines to review available literature(8,44,47,49–51). Other public databases utilized include COSMIC (cancer.sanger.ac.uk/cosmic), cBio (www.cbioportal.org), ClinGen (www.clinicalgenome.org), UniProt (www.uniprot.org), ClinVar (www.ncbi.nlm.nih.gov/clinvar), 1000 Genomes (www.internationalgenome.org), and dbSNP (www.ncbi.nlm.nih.gov/projects/SNP). Although these resources are important, they are not necessarily designed for point of care clinical use. This underscores the need for specialized processes to review and interpret the existing molecular knowledge-bases. Several groups have therefore developed publically-available resources to help organize and interpret the immense amount of existing molecular data.

Some of the most prominent publically-available precision oncology websites are listed in Table 3. Although most include similar general information, important differences between the websites include content organization, the ability to search for clinical trials, and the level of detail provided. There are also differences in algorithms for deciding which data to include and the definitions of actionability. At present, no direct comparisons of these resources exist, and thus the choice of which website to use depends on users' individual needs and preferences. While creating and maintaining these publically-available resources is a time-consuming and labor-intensive process, such resources can help bridge the gap between research and practice, particularly when on-site precision oncology support services are not available.

Many providers or institutions have alternatively sought assistance from centralized decision support services. Selected commercial services are listed in Supplemental Table 2.

Molecular Tumor Boards

Many institutions have established Molecular Tumor Boards (MTBs) to help interpret the increasing amount of data available(8,16,43–48,52–54). MTBs are frequently multidisciplinary, and include oncologists, research scientists, bioinformaticians, and genetic counselors(47,53,55).

Most MTBs review a patient's clinical, pathologic, and molecular information, and ultimately make therapy recommendations that include clinical trial options, use of FDA-approved agents on-label, and occasionally use of investigational agents on a compassionate IND or off-label use of FDA-approved therapies (45–47,49,52,54,56,57). Although clinical trials are potentially the most desirable strategy, studies show that the percentage of patients treated on genomically-driven clinical trials is low (2–18%)(15,46,49,52,56). In recent studies, the proportion of patients whose treatment decision was impacted by genomic testing was 5–40%(5,46,47,52,53,55,56), reflecting many challenges to the routine practice of precision oncology.

As genomic testing becomes more widely available, approaches such as MTBs are unlikely to be scalable. Ideally, available molecular data would be incorporated into existing treatment planning conferences and day-to-day clinical workflow, with point of care decision support.

Institutional Decision Support Services

Several large institutions have created teams to centralize genomic interpretation and provide decision support. At The University of Texas MD Anderson Cancer Center, we have set up a Precision Oncology Decision Support (PODS) team in order to facilitate therapeutic decision-making(39). The PODS team maintains highly curated databases for gene-variants, functional genomics, drugs, and clinical trials, as previously described(58,59). Our current list of actionable genes is available in Supplemental Table 3, but is continuously evolving.

Most decision support requests are for interpretation of genomic results. Clinicians can choose to either interpret the genomic data on their own, or can request an annotation by the PODS team. A conceptual model of the annotation process is shown in Figure 2. Once

completed, the annotation is made available via the electronic health record(59). The PODS team also informs the requesting clinician of any actionable alterations and relevant clinical trials(39). Turnaround time for annotation is critical for maintaining clinical utility and we have strived to bring this time down to less than 24 hours, preferably within hours. We expect to transition to routine annotation of testing performed in-house soon, but expect that point-of care services will still be desired for testing performed elsewhere.

At this time, the PODS team has received over 3,629 annotation requests on 2,741 patients with over 50 tumor types(59). The first 2,444 PODS annotations performed for 669 patients that included an actionable variant call were recently reviewed: 32.5% were actionable, 9.4% potentially actionable, 29.7% unknown, 28.4% non-actionable(59). Of patients with actionable or potentially actionable alterations, 20.6% enrolled on a genomically-matched trial. Trial enrollment was higher for actionable/potentially actionable alterations (27.6%) than those with unknown (11.8%) and non-actionable (3%) alterations (p=0.00004). This demonstrates the interest in and perceived value of decision support, even in academic settings with highly specialized oncologists. Decision support needs in the community may be even higher, with the caveat that therapeutic options may be more limited due to lack of access to trials.

DECISION SUPPORT EFFORTS IN PRECISION ONCOLOGY TRIALS

Decision Support in Precision Oncology Trials

There are now also several large multicenter precision oncology studies. We will highlight four important examples to demonstrate decision support approaches utilized.

NCI-MATCH (Molecular Analysis for Therapy Choice, NCT02465060) is a prospective precision oncology trial in which patients are assigned to receive treatment based on alterations found in their tumors through genomic sequencing (and a few IHC assays) (57,60). Treatment decisions are based upon pre-determined algorithms (MATCHBOX)(57), with review of matches by a multidisciplinary team including oncologists, informaticians, and pathologists.

NCI-MPACT (NCT01827384) is a randomized, biomarker-driven clinical trial. It uses next-generation sequencing to evaluate for alterations impacting RAS/RAF/MEK, PI3K, and DNA damage repair(61). Pre-specified rules designate alterations as being actionable. For the study, the NCI developed a system called GeneMed, which helps to determine appropriate treatment allocation(61). GeneMed automatically identifies suspected actionable alterations, which are then individually reviewed. These data are then used to randomize the patient. Automating part of the process reduces the burden on the decision support team, and standardizes the definition of actionability across sites.

ASCO’s Targeted Agent and Profiling Utilization Registry (TAPUR) is also ongoing. The goal of this registry study is to describe drug activity and toxicity for novel agents used in the setting of an actionable variant(62). This study has the potential to increase access to targeted agents and precision oncology decision support to community oncology providers as well as participating academic centers. In this study, the provider can make the initial

determination for patient eligibility and receive central confirmation(62). However, a Molecular Tumor Board which is organized by ASCO is also available for consultation. All drugs are provided by the pharmaceutical companies, and all data are collected and monitored centrally. In addition to providing important toxicity and efficacy information, this study will also assess practitioner knowledge.

Similar trials are also currently being conducted successfully outside of the United States. The WINTHER study is one such study which serves as an interesting model for incorporating transcriptomics into treatment decisions(63). WINTHER also highlights some of the considerations relevant to future international collaborations for precision oncology decision support. Specifically, attention to differences in regulatory testing requirements across countries and barriers to using similar platforms under different regulatory environments will be important for future trials(63).

CHALLENGES TO PRECISION ONCOLOGY DECISION SUPPORT

Expanding Available Biomarkers

Information about transcriptional output, protein expression, epigenetic modifications, and metabolomics may provide a broader understanding of mechanisms of tumor growth, and allow for better treatment decisions(8,32,64). Although difficulties with RNA preservation in formalin-fixed paraffin embedded tissues persist(65), approaches such as RNAseq are now transitioning to the CLIA environment. Further investigation into optimizing techniques for functional proteomics or to operationalize use of multiplex immunohistochemistry will be critical(66). Once these technologies are implemented in the clinical setting, however, the need for scientific and bioinformatics support will only increase.

Patients with multiple alterations remain another challenge. Targets often are prioritized, taking into consideration the allelic frequency of different alterations, relative copy number gain/loss for copy number alterations, and level of evidence of therapeutic implications. Sometimes the presence of a second alteration is thought to be a contraindication for acting on the first alteration (as in the case of activating mutation of *EGFR* and *KRAS*). This problem of multiple alterations is likely to grow with broader testing panels. However, multianalyte testing may further assist in decision-making by elucidating which downstream pathway is activated, etc.

Immunotherapy is also a growing field. Although many of the decision support criteria may be different, the precepts underlying the importance of decision support are the same. Biomarkers that predict sensitivity or resistance to immunotherapies are starting to be developed including tumor mutation burden, neoantigen load, neoantigen expression, tumor infiltration lymphocytes, CD8+ cells, PDL1 expression, and immune infiltrate gene expression signatures. However, some are still controversial (e.g., PDL1) and others are not readily available on all tumor types (tumor mutation burden)(67). Although the predictive value of genomics and other multianalyte techniques have shown promise, this work is still in its infancy as compared with biomarker discovery for targeted therapies(68,69). As indications and therapeutic approaches for immunotherapy continue to grow, it is imperative

that precision oncology decision support services are equipped to interpret these classes of biomarkers.

Operational Considerations

Cost is an ongoing barrier for precision oncology. Although the cost of next-generation sequencing is decreasing(70), new technologies are continuously being developed. As a field, there is interest in broadening molecular testing for patients in order to address clonal evolution and molecular heterogeneity. However, this will also increase both the amount of data, and the frequency at which data must be analyzed. Furthermore, questions about insurance coverage of testing persist, despite increased use of sequencing in oncologic care(52,71). Additionally, the cost of maintaining decision support infrastructure itself must also be taken into account(72).

Access to investigational therapies through clinical trials is also relevant. The large number of exclusions to eligibility can limit the ability of patients with genomic aberrations to receive matched therapies. Additionally, insurance concerns about enrollment on trials persist. Clinical trial access is also related to geographic limitations, as a large proportion of cancer patients live a burdensome distance from the closest trial site(73). Novel precision oncology initiatives such as ASCO's TAPUR study will enhance access to off-label drugs while ensuring oncologic outcomes are collected.

The institutional nature of most precision oncology decision support services is both an asset and a weakness. With local review, recommendations are based upon the specific needs and resources of that institution. However, much of the same work is done independently by many institutions. Multiple institutions maintain their own databases for research, including evolving information about actionability and available clinical trials. While this state of decentralized science is not limited to precision oncology, it does limit scalability and reproducibility. However, there are also financial, academic, and logistical incentives for maintaining separate databases and knowledgebases. Regardless, increasing efficiency and decreasing cost of decision support services will be necessary for precision oncology to become the new model for oncology care.

CONCLUSION

Precision oncology is an exciting and rapidly evolving field. With a greater number of therapies and diagnostics, there is a critical need for precision oncology decision support. As our ability to target specific pathways improves, so too must our processes for identifying appropriate patients. "All-comer" trials are increasingly replaced by molecularly-matched clinical trials. While this is likely to improve clinical outcomes, it also means that the knowledge required to practice oncology is becoming increasingly complex. Thus, more sophisticated and organized precision oncology decision support services is critical to implementing precision oncology in routine cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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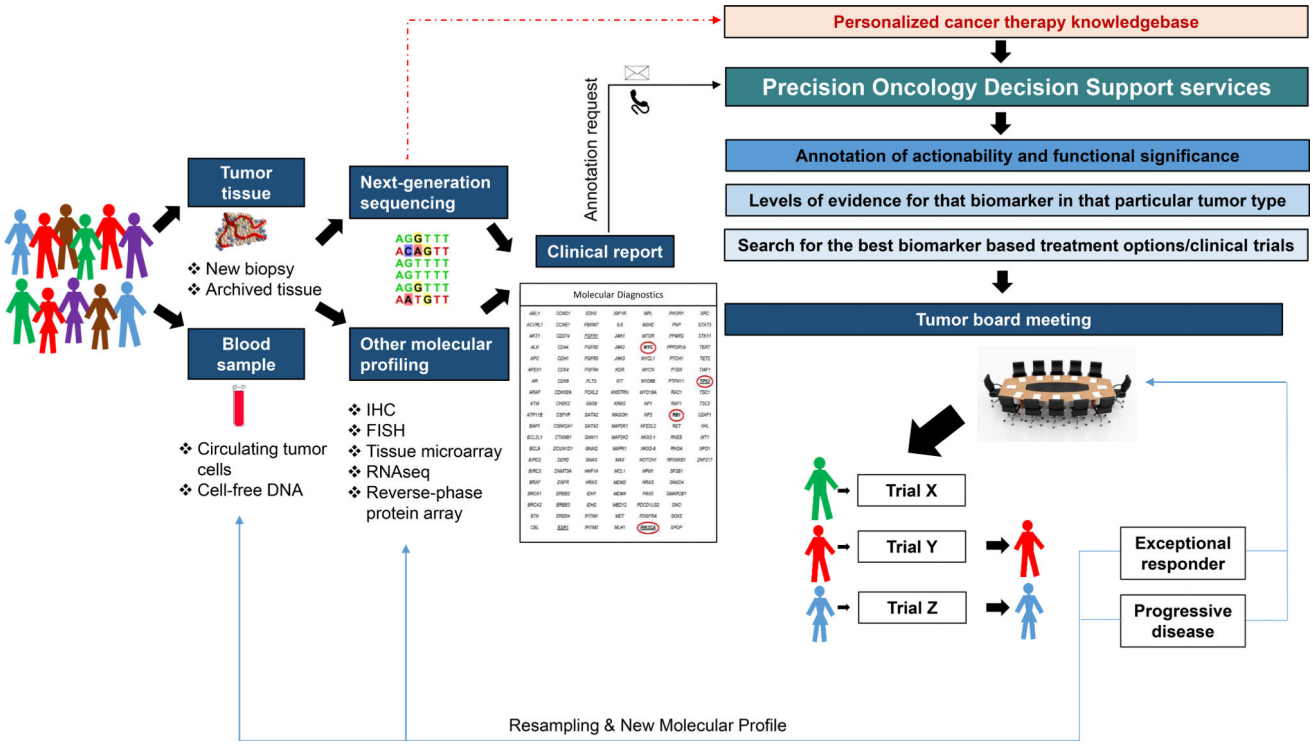

Figure 1.

A flow diagram of precision oncology services that an individual patient may receive while being considered for a targeted agent or investigational therapy.

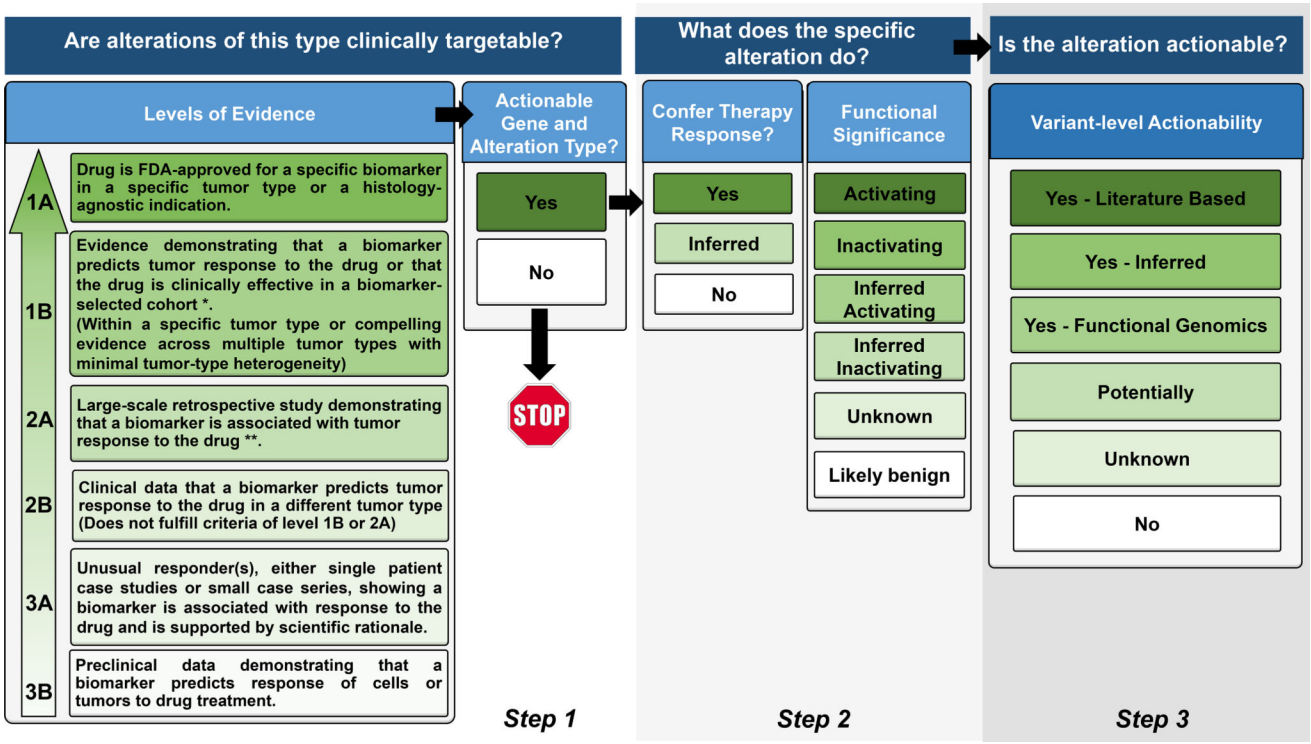

Figure 2.

Procedural flow used by the Precision Oncology Decision Support (PODS) team at MD Anderson Cancer Center for annotating an alteration. Our tiers for Levels of Evidence, Functional Significance, and Variant Level of Actionability are included. Terminology is defined in Supplemental Table 1.

* For Level of Evidence 1B, “Evidence” could be:

- An adequately-powered, prospective study with biomarker selection/stratification
- A meta-analysis/overview
- A consensus recommendation for standard of care (as recommended by NCCN guidelines or other consortia)

** For Level of Evidence 2A, “Evidence” could be:

- A prospective trial where biomarker study is the secondary objective
- An adequately-powered retrospective cohort study
- An adequately-powered case-control study

Table 1

Food and Drug Administration (FDA) approved targeted therapies for tumors that have an associated biomarker.

Preferred Name	Direct drug Target	Company	FDA Approved Indication - Disease(s)	FDA Approved Indication - Biomarker(s)
Abemaciclib	CDK4, CDK6	Eli Lilly and Company	Breast cancer	ER Positive, PR Positive, HER2 Negative
Afatinib	EGFR	Boehringer Ingelheim	Non-small cell lung carcinoma	EGFR Deletion Exon 19, EGFR L858R
Alectinib	EML4-ALK, ALK, INSR, RET	Genentech	Non-small cell lung carcinoma	ALK Fusion
Anastrozole	Aromatase	AstraZeneca Pharmaceuticals	Breast cancer	ER Positive, PR Positive
Bosutinib	ABL1, BCR-ABL1, SRC	Pfizer	Chronic myelogenous leukemia	BCR-ABL1
Brigatinib	ALK, CSF1R, INSR, ABL1, LCK, IGF1R, CAMK2G, FLT4, RET, FGFR1, FGFR2, FGFR3, AURKA, JAK2, FGFR4, FYN, HCK, LYN, SRC, EGFR, EML4-ALK, FER, FES, FLT3, FPS, ROS1, TYK2, YES1, PTK2B, HER4, CAMK2D, CHEK1, CHEK2	Ariad Pharmaceuticals	Non-small cell lung carcinoma	ALK Fusion
Ceritinib	NPM-ALK, ROS1 Fusion, ALK, INSR, IGF1R, TSSK3, FLT3, FGFR2, RET, FGFR3, LCK, JAK2, AURKA, LYN, EGFR, FGFR4	Novartis Pharmaceuticals	Non-small cell lung carcinoma	ALK Fusion
Cetuximab	EGFR	Eli Lilly and Company	Colorectal cancer	KRAS Wildtype, EGFR Positive
Cobimetinib	MAP2K1	F. Hoffmann-La Roche	Melanoma	BRAF V600E, BRAF V600K
Crizotinib	ALK, MET, ROS1, NTRK1	Pfizer	Non-small cell lung carcinoma	ALK Fusion
		Pfizer	Non-small cell lung carcinoma	ROS1 Positive
Dabrafenib	BRAF, RAF1	GlaxoSmithKline	Melanoma	BRAF V600E
		GlaxoSmithKline	Melanoma	BRAF V600E, BRAF V600K
		GlaxoSmithKline	Non-small cell lung carcinoma	BRAF V600E
Dasatinib	ABL1, KIT, BRAF, BCR-ABL1, ABL2, PDGFRA, PDGFRB, SRC, DDR1, DDR2, EPHA3 Amplification, EPHA2, FYN, LCK, LYN, YES1	Bristol-Myers Squibb	Chronic myelogenous leukemia	BCR-ABL1
			Acute lymphoblastic leukemia	BCR-ABL1
Enasidenib	IDH2	Agios Pharmaceuticals	Acute myeloid leukemia	IDH2 Mutation
Erlotinib	EGFR	Genentech	Non-small cell lung carcinoma	EGFR Deletion Exon 19, EGFR L858R

Preferred Name	Direct drug Target	Company	FDA Approved Indication - Disease(s)	FDA Approved Indication - Biomarker(s)
Everolimus	MTOR	Novartis Pharmaceuticals	Breast cancer	ER Positive, PR Positive, HER2 Negative
Exemestane	Aromatase	Pfizer	Breast cancer	ER Positive
Fulvestrant	ER	AstraZeneca Pharmaceuticals	Breast cancer	ER Positive, PR Positive, HER2 Negative
			Breast cancer	ER Positive, PR Positive
Gefitinib	EGFR	AstraZeneca Pharmaceuticals	Non-small cell lung carcinoma	EGFR Deletion Exon 19, EGFR L858R
Gemtuzumab Ozogamicin	CD33	Pfizer	Acute myeloid leukemia	CD33 Positive
Ibrutinib	TEC, ABL1, FYN, RIPK2, SRC, LYN, PDGFRA, HER2, BTK, EGFR, BLK, BMX, CSK, FGR, PTK6, HCK, YES1, ITK, JAK3, FRK, LCK, RET, FLT3	Janssen Biotech|Pharmacyclics	Small lymphocytic lymphoma, Chronic lymphocytic leukemia	c.CHR17p Deletion
Imatinib	PDGFRA, KIT, BCR-ABL1, ABL1, PDGFRB	Novartis Pharmaceuticals	Gastrointestinal Stromal Tumors	KIT Positive
			Chronic myeloid leukemia, Acute lymphoblastic leukemia,	BCR-ABL1
			Myelodysplastic/myeloproliferative diseases	PDGFRA Fusion
			Chronic eosinophilic leukemia	FIP1L1-PDGFRA
Lapatinib	EGFR, HER2, HER4	Novartis Pharmaceuticals	Breast cancer	HER2 Positive
			Breast cancer	ER Positive, PR Positive, HER2 Positive
Letrozole	Aromatase	Novartis Pharmaceuticals	Breast cancer	ER Positive, PR Positive
Midostaurin	KDR, FLT3, PDGFRA, PDGFRB, SYK, AKT1, FLT1, AKT2, AKT3, KIT, SRC, PRKCA, PRKCB, PRKCG, CDK1, FGR, ETV6-NTRK3	Novartis Pharmaceuticals	Acute myeloid leukemia	FLT3 Mutation
Neratinib	HER2, EGFR, KDR	Puma Biotechnology, Inc.	Breast cancer	HER2 Overexpression, HER2 Amplification
Nilotinib	BCR-ABL1	Novartis Pharmaceuticals	Chronic myelogenous leukemia	BCR-ABL1
Olaparib	PARP1, PARP2	AstraZeneca Pharmaceuticals	Ovarian cancer	BRCA1 (any deleterious), BRCA2 (any deleterious)
Osimertinib	EGFR, EGFR T790M, EGFR Exon 19 deletion	AstraZeneca Pharmaceuticals	Non-small cell lung carcinoma	EGFR T790M
Palbociclib	CDK4, CDK6	Pfizer	Breast cancer	ER Positive, PR Positive, HER2 Negative
Panitumumab	EGFR	Amgen	Colorectal cancer	KRAS Wildtype, NRAS Wildtype

Preferred Name	Direct drug Target	Company	FDA Approved Indication - Disease(s)	FDA Approved Indication - Biomarker(s)
Pertuzumab	HER2	Genentech	Breast cancer, Inflammatory breast cancer	HER2 Positive
Ponatinib	PDGFRA, KDR, SRC, ABL1, FGFR1, BCR-ABL1, KIT, RET	Ariad Pharmaceuticals	Acute lymphoblastic leukemia / lymphoblastic lymphoma, Chronic myeloid leukemia	BCR-ABL1 T315I
			Chronic myeloid leukemia, Acute lymphoblastic leukemia	BCR-ABL1
Ribociclib	CDK4, CDK6	Novartis Pharmaceuticals	Breast cancer	ER Positive, PR Positive, HER2 Negative
Rituximab	CD20	Genentech	Non-Hodgkin's lymphoma, Chronic lymphocytic leukemia	CD20 Positive
Rucaparib	PARP1	Clovis Oncology	Ovarian cancer	BRCA1 (any deleterious), BRCA2 (any deleterious)
Tamoxifen	ER	AstraZeneca Pharmaceuticals	Breast cancer	ER Positive (may help predict whether therapy will be beneficial)
Trametinib	MAP2K1, MAP2K2	GlaxoSmithKline	Melanoma	BRAF V600E, BRAF V600K
			Non-small cell lung carcinoma	BRAF V600E
Trastuzumab	HER2	Genentech	Breast cancer, Gastric cancer, Gastroesophageal junction	HER2 Positive
Trastuzumab Emtansine	HER2, p.Tubulin	Genentech	Breast cancer	HER2 Positive
Vemurafenib	BRAF V600E	F. Hoffmann- La Roche	Melanoma	BRAF V600E
Venetoclax	BCL2	AbbVie	Chronic lymphocytic leukemia	c.CHR17p Deletion

Table 2

A list of actionable genes, the alteration types, and the alteration frequencies for several common cancer types.

Tumor type	Actionable genes	Alteration type	Frequency	Comments
Non-small cell lung cancer	BRAF	Mutations	5–10%	
	DDR2	Mutations	1–6%	
	EGFR	Mutations	4–18%	
	EML4-ALK	Fusion	4%	
	ERBB2	Mutations	2–3%	
	FGFR1	Amplification	2–17%	
	FGFR3	Fusion	2%	
	KRAS	Mutations	1–32%	1% in adenocarcinoma, 32% in squamous cell carcinoma
	MAP2K1	Mutations	1%	
	MET	Amplification	1–4%	
	MET	Mutations	3–8%	3% MET exon 14 mutation in lung adenocarcinoma
	NF1	Mutations	11%	
	NTRK1	Fusion	2–4%	
	PIK3CA	Mutations	4–16%	
	PTEN	Mutations/Deletion	1–8%	
	RET	Fusion	2–4%	
	RICTOR	Amplification	2–5%	
	ROS1	Fusion	4–11%	
	STK11	Mutations	2–17%	
Bladder	AKT1	Mutations	3%	
	CDKN2A	Deletion	47%	
	CDKN2A	Mutations	5%	
	EGFR	Amplification	11%	
	ERBB2	Amplification	7%	
	ERBB3	Mutations	11%	
	FGFR3	Mutations	45%	60–80% in non-muscle-invasive; 15–20% in muscle-invasive bladder cancer
	FGFR3	Amplification	3%	
	FGFR3-TACC3	Fusion	5%	
	KRAS	Mutations	4%	
	MDM2	Amplification	9%	
	PIK3CA	Mutations	20%	
	PTEN	Mutations	3%	
	PTEN	Deletion	13%	
	TSC1	Mutations	9%	

Tumor type	Actionable genes	Alteration type	Frequency	Comments
Biliary	BRAF	Mutations	7%	
	EGFR	Mutations/Amplification	5%	
	ERBB2	Mutations/Amplification	4–18%	18% in gallbladder carcinoma
	FGF19	Amplification	3%	
	FGFR1	Mutations/Amplification	4%	
	FGFR2	Fusion	5%	5% in intrahepatic cholangiocarcinoma
	IDH1/2	Mutations	0–6%	4–6% in intrahepatic cholangiocarcinoma
	KRAS	Mutations	18%	
	MDM2	Amplification	5%	
	PIK3CA	Mutations	7%	
	PTEN	Deletion	1–7%	7% in gallbladder carcinoma
Gastric	EGFR	Mutations	3–5%	
	EGFR	Amplification	6%	
	ERBB2	Mutations	5–7%	
	ERBB2	Amplification	13%	
	ERBB3	Mutations	5–11%	
	ERBB3	Amplification	4%	
	FGFR1	Mutations	4%	
	FGFR2	Amplification	5%	
	KRAS	Mutations	6%	
	MET	Mutations	2%	
	MET	Amplification	4%	
	PIK3CA	Mutations/Amplification	24%	42% and 72% in MSI-H and EBV+ gastric cancer, respectively
	PTEN	Mutations	4–8%	
	PTEN	Deletion	4%	
Melanoma	BRAF	Mutations	45%	
	CDKN2A	Deletion	13%	
	IDH1	Mutations	6%	
	KDR	Amplification	3%	
	KIT	Amplification	4%	
	MAP2K1	Mutations	5%	
	NF1	Mutations	14%	
	NRAS	Mutations	10–25%	
	PDGFRA	Amplification	3%	
Breast	11q	Amplification	15%	
	AKT1	Mutations	2–4%	
	CDKN2A	Deletion	3–4%	

Tumor type	Actionable genes	Alteration type	Frequency	Comments
	ERBB2	Mutations/Amplification	13%	
	ESR1	Mutations	10%	ER+ breast cancer, metastatic samples and not primary (marker of resistance to antiestrogen therapy)
	FGFR1	Amplification	10–15%	
	FGFR2	Amplification	4%	
	MAP2K4	Mutations	2–7%	
	MAP3K1	Mutations	4–13%	
	NF1	Mutations	2–4%	
	NTRK3	Fusion	92%	Secretory breast cancer
	PIK3CA	Mutations	9–45%	
	PIK3CA	Amplification	4–5%	
	PIK3R1	Mutations	2%	
	PTEN	Mutations/Deletion	3–8%	
	RB1	Mutations/Deletion	5–6%	Marker of resistance to CDK 4/6 inhibitors
Colorectal	AKT1	Mutations	1–6%	
	BRAF	Mutations	3–47%	47% in MSI-H colorectal cancer
	ERBB2	Mutations/Amplification	6–13%	
	ERBB3	Mutations	4–20%	
	KRAS	Mutations	35%	
	NRAS	Mutations	10%	
	PIK3CA	Mutations	15–37%	37% MSI-H colorectal cancer
	PIK3R1	Mutations	2–17%	
	PTEN	Deletion	4–20%	20% MSI-H colorectal cancer
Ovarian	AKT1	Amplification	3%	
	AKT2	Amplification	2%	
	BRAF	Mutations	2–6% (low grade serous ovary)	Extremely rare in high grade ovarian cancer; 2–6% low grade serous ovarian cancer (excluding borderline tumors)
	BRCA1 (germline or somatic)	Mutations	9%	
	BRCA2 (germline or somatic)	Mutations	5%	
	CCND1	Amplification	20%	
	CDKN2A	Deletion	32%	
	FGFR1	Amplification	5%	
	KRAS	Mutations/Amplification	19–33% (low grade serous ovary)	Extremely rare in high grade; 19–33% low grade serous ovarian cancer (excluding borderline tumors)
	NF1	Mutations/Deletion	12%	

Tumor type	Actionable genes	Alteration type	Frequency	Comments
	NOTCH3	Mutations/Amplification	11%	
	PIK3CA	Mutations/Amplification	18%	
	PTEN	Mutations/Deletion	7%	
Glioblastoma	BRAF	Mutations	2%	
	CDK4	Amplification	14%	
	CDK6	Amplification	2%	
	CDKN2A/B	Deletion	61%	
	EGFR	Mutations	17–21%	
	EGFR	Amplification	41–44%	
	FGFR1-TACC1	Fusion	NA	
	FGFR3-TACC3	Fusion	3–7%	
	IDH1	Mutations	5–12%	
	MDM2	Amplification	7%	
	MDM4	Amplification	8%	
	MET	Amplification	2%	
	NF1	Mutations	10%	
	NTRK1	Fusion	1%	
	PDGFRA	Amplification	10%	
	PIK3CA	Mutations/Amplification	25%	
	PTEN	Mutations/Deletion	41%	

MSI-H = Microsatellite instability high; EBV = Epstein-Barr Virus

Table 3

Select publically-available precision oncology decision support websites.

Website	Maintained by	Number of genes	Organized by gene?	Organized by tumor type?	Clinical trials?
Personalized Cancer Therapy www.personalizedcancertherapy.org (Accessed: 26 June 2017)	The University of Texas MD Anderson Cancer Center	30	Yes	No: tumor-specific information listed within the gene page	Yes: searchable by gene
My Cancer Genome www.mycancergenome.org (Accessed: 26 June 2017)	Vanderbilt-Ingham Medical Center	823	No: must search by tumor type (except trials)	Yes	Yes: searchable by gene and tumor type
OncoKB oncokb.org (Accessed: 26 June 2017)	Memorial Sloan Kettering Cancer Center, partnership with Quest Diagnostics	476	Yes	No: frequency data for tumor types listed within the gene page	No
Precision Cancer Medicine www.precisioncancermedicine.org (Accessed: 26 June 2017)	Dana Farber/Brigham and Women's Cancer Center	17	No	Yes: clinical trials organized primarily by tumor type	Yes: limited to those offered at Dana Farber
Drug Gene Interaction Database dgidb.genome.wustl.edu (Accessed: 26 June 2017)	Washington University in St. Louis	8,419	Yes	No: would need to review references for tumor type information	No