PRECISION MEDICINE

review articles

An Approach to Solving the Complex Clinicogenomic Data Landscape in Precision Oncology: Learnings From the Design of WAYFIND-R, a Global Precision Oncology Registry

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abstract

Precision oncology, where patients are given therapies based on their genomic profile and disease trajectory, is rapidly evolving to become a pivotal part of cancer management, supported by regulatory approvals of biomarker-matched targeted therapies and cancer immunotherapies. However, next-generation sequencing (NGS)–based technologies have revealed an increasing number of molecular-based cancer subtypes with rare patient populations, leading to difficulties in executing/recruiting for traditional clinical trials. Therefore, approval of novel therapeutics based on traditional interventional studies may be difficult and time consuming, with delayed access to innovative therapies. Real-world data (RWD) that describe the patient journey in routine clinical practice can help elucidate the clinical utility of NGS-based genomic profiling, multidisciplinary case discussions, and targeted therapies. We describe key learnings from the setup of WAYFIND-R (NCT04529122), a first-of-its-kind global cancer registry collecting RWD from patients with solid tumors who have undergone NGS-based genomic profiling. The meaning of 'generalizability' and 'high quality' for RWD across different geographic areas was revisited, together with patient recruitment processes, and data sharing and privacy. Inspired by these learnings, WAYFIND-R's design will help physicians discuss patient treatment plans with their colleagues, improve understanding of the impact of treatment decisions/cancer care processes on patient outcomes, and provide a platform to support the design and conduct of further clinical/epidemiologic research. WAYFIND-R demonstrates user-friendly, electronic case report forms, standardized collection of molecular tumor board-based decisions, and a dashboard providing investigators with access to local cohort-level data and the ability to interact with colleagues or search the entire registry to find rare populations. Overall, WAYFIND-R will inform on best practice for NGS-based treatment decisions by clinicians, foster global collaborations between cancer centers and enable robust conclusions regarding outcome data to be drawn, improve understanding of disparities in patients' access to advanced diagnostics and therapies, and ultimately drive advances in precision oncology.

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CURRENT CHALLENGES WITH PRECISION ONCOLOGY

Precision oncology, where patients are given therapies on the basis of their genomic profile and disease trajectory, is rapidly evolving to become a pivotal part of cancer management, supported by the approval of many biomarker-matched targeted therapies and cancer immunotherapies by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).[1] Driven by recent advances in diagnostics, especially next-generation sequencing (NGS)–based technology using liquid- and solid-based biopsies, precision oncology has revealed the complexity of the genomic landscape of various cancer types. For example, a pan cancer whole-genome analysis of metastatic tumors found an alteration in oncogenic drivers in more than 98% of samples.[2] Furthermore, in the National Cancer Institute Molecular Analysis for Therapy Choice trial of tumor biopsy specimens from 5,954 patients with refractory malignancies, an actionable alteration was found in 37.6% of patients while just 17.8% had an alteration that could actually be matched with an investigational or FDA-approved drug, after application of clinical and molecular exclusion criteria.[3] As further potential genomic markers are discovered, the size of the target population reduces, and the number of patients with an alteration that matches therapy assignment in a given tumor type can be extremely low.

The small population of patients with unique actionable mutations suggests that, for precision oncology

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CONTEXT

Key Objective

WAYFIND-R (ClinicalTrials.gov identifier: NCT04529122) is a first-of-its-kind global cancer registry collecting real-world data (RWD) from patients with solid tumors who have undergone next-generation sequencing–based genomic profiling. How can learnings from WAYFIND-R aid the continual adaptation of clinical practice of precision oncology?

Knowledge Generated

The meaning of generalizability and high quality for RWD across different geographic areas was revisited, together with patient recruitment processes and data sharing and privacy. These learnings have shown that it is possible to collect high-quality RWD, thus improving the acceptance and success of WAYFIND-R itself.

Relevance

WAYFIND-R will inform on best practice for next-generation sequencing–based treatment decisions by clinicians, foster global collaborations between cancer centers and thereby enable robust conclusions regarding outcome data to be drawn, improve understanding of disparities in patients' access to advanced diagnostics and therapies, and ultimately drive progress in precision oncology.

clinical trials investigating targeted therapies and cancer immunotherapies, recruitment is challenging, and trials are likely to be statistically underpowered to demonstrate acceptable safety and efficacy. Consistent with this, recruitment rates in molecularly matched clinical trials in a reference institution have dropped from 15% in 2016 to 11% in 2017 and 2018, despite an increase in the number of trials and drug targets.[4]

The challenge with designing precision oncology–based clinical trials is also confounded by ethical concerns related to running placebo-controlled trials, a lack of information on understanding the natural history of patients with solid tumors expressing these alterations, and inabilities to meet the regulatory requirements for drug approval.[4,5] Furthermore, whereas cancer clinical trials typically have a high internal validity, they face issues of external validity. Approximately 8% of adult patients with cancer in the United States participate in a clinical trial,[6] and interventional trials usually focus on a single alteration with narrow patient eligibility criteria; therefore, it is unclear how applicable results from a clinical trial are in a real-world setting.[7,8] Clinical trials and registries in precision oncology have also been found to vastly underrepresent racial and ethnic minority populations, such as Black and Hispanic participants, relative to their cancer incidence.[9] Overall, generating large clinical trial evidence in a pan cancer setting is challenging or sometimes not possible, leading to limited knowledge of the efficacy and safety of targeted therapies and cancer immunotherapies across different cancer types in routine clinical practice.[8,10] Therefore, approval of such novel therapeutics on the basis of traditional interventional studies may be difficult and time-consuming, with delayed access to innovative therapies.

Besides difficulties in executing and recruiting for clinical trials, precision oncology also faces challenges associated with making decisions regarding targeted therapies and cancer immunotherapies in the real world once alterations have been detected in a patient's tumor. Classification systems have been developed to rank alterations for precision oncology on the basis of the current clinical evidence of their actionability (eg, European Society for Medical Oncology Scale for Clinical Actionability for molecular Targets).[11] However, the validity of these frameworks for therapy prioritization in an investigational setting still needs to be demonstrated.[12]

To aid therapy decision-making in precision oncology, molecular tumor boards (MTBs), which include a range of clinical and molecular expertise, are critical.[13] However, there remain differences in precision oncology approvals between the FDA and EMA, sometimes causing difficulties for clinical actionability.[14] Therefore, application of MTBs requires standardization of current precision oncology approvals and further evidence for clinicians to guide therapy decisions after NGS test results in the real world, especially in rare cancers and tumors with a low prevalence of genomic alterations.[15] Furthermore, the positive impact of an MTB-based, precision medicine approach from the MOSCATO,[16] WINTHER,[17] and iPREDICT[18] studies are test-driven academic cohorts with access to phase I trials and are not representative of (and possibly not reproducible in) nonacademic, community oncology practices.

IMPORTANCE OF REAL-WORLD DATA IN PRECISION ONCOLOGY

The term real-world data (RWD) is defined by the FDA as data relating to a patient's health status and/or the delivery of health care routinely collected from a variety of sources.[19,20] RWD have a wide variety of applications; for example, it can expand upon clinical trial results to confirm/assess efficacy and long-term safety of a therapy in a much broader and more generalizable patient population, assess several different lines of therapies in molecularly defined populations, and offer insights into rare tumors (eg, GI stromal tumors)[21-23] and rare events or patient populations not normally included in clinical trials (eg, elderly patients with comorbidities).[24] Furthermore, RWD can be used to

identify patients treated with alternative therapies, who form a control (comparator) arm for single-arm clinical trials of experimental agents in rare cancer types, in which randomized controlled trials are not feasible. These key insights may offer many benefits, as highlighted in Table 1.

Patient registries, electronic health records, or wearables represent potential sources of RWD.[15] In particular, registries are defined by the EMA as organized systems that use observational methods, followed over time, to collect uniform data on a patient population defined by a particular disease, exposure, or condition (eg, age, pregnancy, and specific patient characteristics).[33] Multiple cancer registries are ongoing, including the American Association for Cancer Research Project GENIE, a publicly accessible international cancer registry of RWD.[34] GENIE links clinical grade, cancer genomic NGS data with clinical outcomes obtained during routine medical practice, focusing on patients with cancer treated at reference academic institutions worldwide with a high expertise in NGS and MTBs.[34] GENIE may represent a biased cohort, given the accessibility to early clinical trials and experimental therapies. Furthermore, GENIE has an overwhelming majority of White participants, thus limiting interracial comparisons of genomic differences and, therefore, efforts to reduce disparities in cancer health outcomes between these populations.[35-37]

However, overall, data in registries and other sources of RWD, although plentiful, are frequently nonstandardized, incomplete, nonaccessible, and siloed, which limits linkage and pooling between data sets and their consequent usefulness in answering particular scientific questions.[8] Measures and processes to ensure data quality or relevancy are often missing.[8] It is also critical for registries to contextualize the patient population with prospectively captured social determinants of health, including health insurance, geographic location, socioeconomic status, and lifestyle, this being key for ensuring benefits of precision oncology reach all but has been poorly studied thus far.[9,38] Furthermore, combining data sets from distinct, previous, and ongoing platforms is challenging because of their heterogeneity in geographic locations, cancer types studied, data elements collected, data quality and terminology, and data sharing and privacy conditions.[33]

A standardized, global data collection platform is thus needed to obtain high-quality RWD from patients with solid tumors who have been profiled with an NGS test (by filling the aforementioned evidence gaps). This may aid our understanding of the most appropriate use, uptake, target population, and changes over time of modern precision oncology tools in clinical practice, when applied in routine care for improved clinical decision-making.

WAYFIND-R: OBJECTIVES AND DESIGN

Developed in accordance with guidance from the EMA, WAYFIND-R is a multicountry, multisite, prospective cancer

TABLE 1. Potential Benefits of RWD in Precision Oncology, With Use Cases

Early- and late-stage clinical development of biomarkers and matched drugs
Inform on treatment gaps and quality of care, thereby enabling patients to access the most appropriate treatment on the basis of evidence generated from both clinical trials and clinical practice. For example, a registry-based study of treatment among 2,445 patients with muscle-invasive bladder cancer in the Netherlands found that one-third of patients did not have definitive treatment with cystectomy or radiotherapy and that a lack of treatment with cystectomy was associated with advanced age and comorbidity.[25] Despite the association of cystectomy with improved survival, this may indicate that it has been underutilized in the elderly and in patients with serious comorbidity, which could further worsen outcomes[25]
Enhance target discovery and understanding of molecular pathways to direct research and development toward areas of unmet need. For example, EHRs have been used within the NIH to differentiate patients' needs and enable the design of trials that accelerate innovative interventions to testing phase in patient subgroups with particular needs[21,26,27]
Support label expansion and potential new drug indications. For example, on the basis of RWD from EHRs in the Flatiron Health Analytic Database and IQVIA, the FDA approved the expansion of the previously approved indication of palbociclib plus an aromatase inhibitor or fulvestrant in women with hormone receptor–positive, HER2-negative, advanced or metastatic breast cancer, to include men (excluded from pivotal trials)[28]
Use as an external control arm to contextualize data from prior, single-arm clinical trials and support drug approvals. For example, the FDA granted accelerated approval in 2019 to entrectinib for the treatment of adults with *ROS1*-positive metastatic NSCLC, with the Genentech, Inc submission package including data from the Flatiron Health Database as an external control arm to support ongoing phase I and II, single-arm trials (ALKA-372-001, STARTRK-1, and STARTRK-2)[29,30]
Commercialization phase
Improve confidence among clinicians in interpreting the results of an NGS test, allowing prescription of the most appropriate treatment for their patient. For example, CancerLinQ, a rapid learning health care system in oncology, is an ASCO initiative that collects information from EHRs of 130,000 patients with breast cancer to provide clinical decision support to practicing oncologists[31]
Inform patients and health care professionals of the value of precision oncology, leading to more innovative contracts and value- and outcomes-based contracting
Provide regulatory authorities with better and earlier understanding of the potential impact and long-term outcomes of targeted therapies and cancer immunotherapies (in molecularly defined populations) to aid postmarketing authorization (eg, osimertinib in metastatic epidermal growth factor receptor *T790M* mutation–positive NSCLC)[32]

Abbreviations: EHR, electronic health record; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor; NGS, next-generation sequencing; NIH, National Institutes of Health; NSCLC, non–small-cell lung cancer; RWD, real-world data.

registry that is collecting data from adult patients who have undergone NGS testing (Fig 1). This registry is focused on solid tumors only, excluding hematologic malignancies as initiatives comparable with WAYFIND-R are already ongoing in the hematology setting (eg, HARMONY).[39]

WAYFIND-R aims to

1. Characterize the treatments and clinical course of patients with solid tumors who have undergone NGS testing.
2. Provide a data research platform to improve understanding of health outcomes, cancer care processes, treatment patterns, and decision-influencing factors in a real-life setting.
3. Support the design and conduct of clinical trials and epidemiologic research.
4. Provide a basis for key learnings related to best practice for facilitating data quality, data sharing, and privacy according to General Data Protection Regulation (GDPR) and/or local requirements.

WAYFIND-R includes both retrospective and prospective data collection, aiming to capture a patient's entire cancer journey from diagnosis until disease resolution or death. The registry initially comprises a pilot phase of academic centers in select European and Latin American countries to assess feasibility of data collection, data quality and relevance of data collected, and data standardization. Upon successful completion of the pilot phase, WAYFIND-R will subsequently be expanded to more countries and sites, including private clinics and community hospitals as well as more academic centers, to increase the representativeness of the registry population. The registry is expected to enroll approximately 15,000 patients in 5 to 6 years. Although initially based outside the United States, WAYFIND-R will seek collaboration with other ongoing initiatives to ensure that it becomes a global, more comprehensive, and dynamic effort that is aligned with the EMA and can be adapted as necessary. Such data linkage is key to ensuring that WAYFIND-R becomes an all-encompassing initiative in the field of precision oncology. Collaboration between efforts will also mean that the standardized data collection in WAYFIND-R according to data models such as the Observational Medical Outcomes Partnership can help to simplify data standardization efforts in other initiatives.

In WAYFIND-R, sites will be chosen where MTBs are in place and where in-person or virtual meetings are held regularly to discuss patient diagnosis and clinical status, genomic profiling, and therapy options. WAYFIND-R will

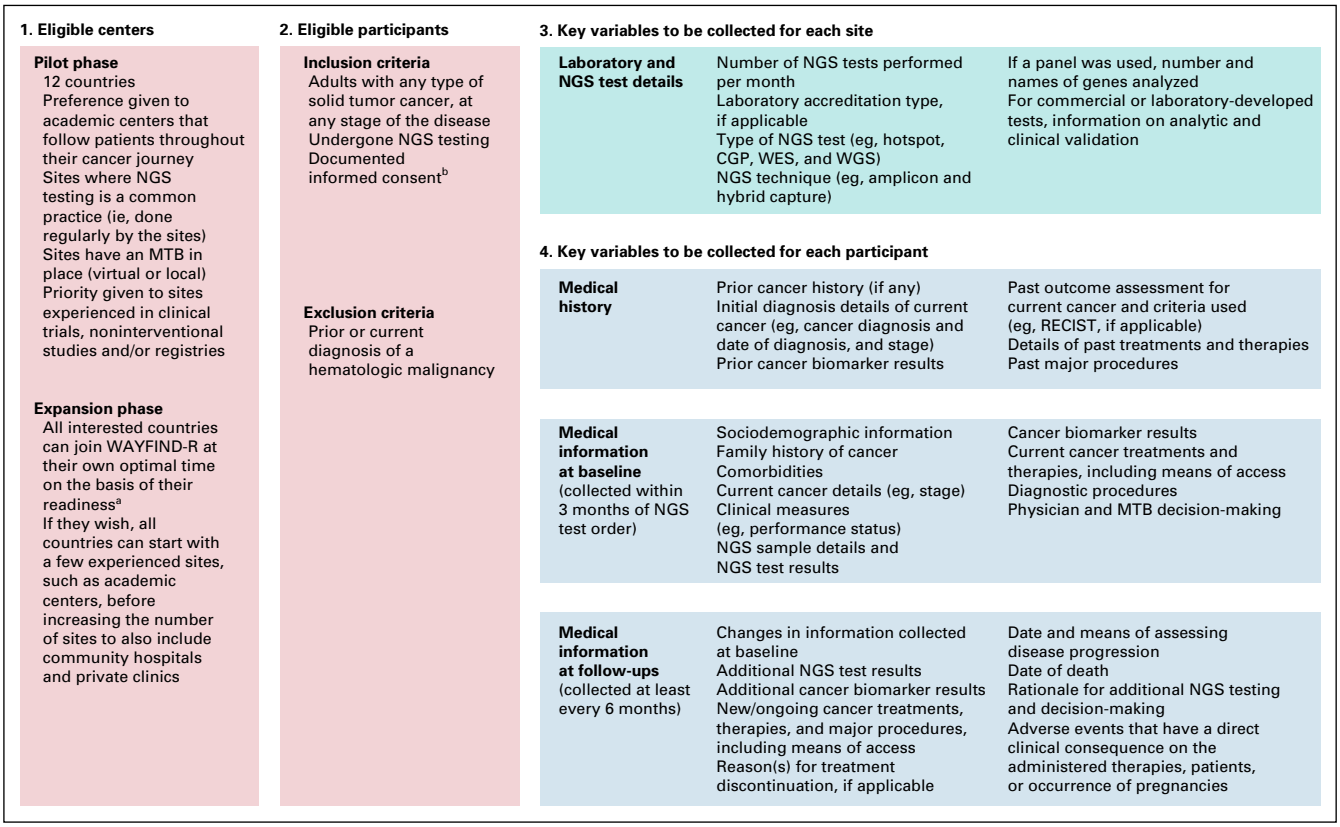

FIG 1. WAYFIND-R design. [a]Readiness is defined by local precision oncology maturity (sufficient uptake of NGS testing, possibility of policy changes, and reimbursement) and how beneficial implementing WAYFIND-R will be at that stage. [b]A signed and dated informed consent form is obtained from patients. The participant must have signed the informed consent form before inclusion and exclusion criteria are checked and confirmed, at which point the patient can be enrolled. CGP, comprehensive genomic profiling; MTB, molecular tumor board; NGS, next-generation sequencing; RECIST, Response Evaluation Criteria In Solid Tumors; WES, whole-exome sequencing; WGS, whole-genome sequencing.

collect variables linked to the decision-making process, including reason for ordering an NGS test, MTB organization, and individual patient recommendations with regards to treatment options. This will aid understanding of differences in health care processes between sites and countries, as well as how such differences may influence patient outcomes.

Sociodemographic information will be collected in WAYFIND-R to contextualize the patient population with social determinants of health (Fig 1). This information will be abstracted from the medical records collected by the registry-treating physician or medical staff and recorded on electronic case report forms (eCRFs). Such contextualization is critical in understanding disparities between different populations in precision oncology–related outcomes and thereby reducing this bias.[9,38]

WAYFIND-R will enable secondary data use studies, to help address a large number of research questions from the original data collected, and ancillary studies, which can be designed to collect new data in defined subpopulations to answer further research questions. For example, ancillary studies can enable collection of patient-reported outcomes and cost-effectiveness studies of targeted therapies and cancer immunotherapies, helping to optimize patient management and site resources.

The global, standardized nature of WAYFIND-R will offer an opportunity for external data sharing and contribution to publications. It will enable sufficiently large sample sizes to address the complexity of genomic profiles and draw robust conclusions related to effectiveness and long-term safety of targeted therapies and cancer immunotherapies. In addition, WAYFIND-R will provide researchers with access to global patient-level data to help answer specific research questions, thus enabling collaboration across different stakeholders with a shared purpose (Fig 2). WAYFIND-R will also provide contributing sites with a visual dashboard that enables physicians to find a similar patient pool across the whole data set to understand their treatment and response patterns, thus providing insights to inform clinical treatment decision-making. Such local, European, and global collaborations will significantly improve implementation, awareness, and understanding of WAYFIND-R to further advance precision oncology. This model will also incentivize physicians to participate in the registry, thereby enlarging patient numbers and enriching data sets to the ultimate benefit of the scientific community and, eventually, patients.

WAYFIND-R: CHALLENGES AND KEY LEARNINGS

The development of the WAYFIND-R registry and its operational implementation has led to many key learnings, including those related to the meaning of generalizability and high quality of RWD across different geographic areas, patient recruitment processes, and data sharing and privacy (Fig 3). These learnings have shown that it is possible to collect high-quality RWD, thus improving the acceptance and success of WAYFIND-R itself. The learnings will also inform on optimal design and management of future, similar initiatives.

Challenge and Learning No. 1: Ensuring a Population and Data Set That is Representative and Generalizable

RWD must be of high generalizability, meaning that the results can be applied to a broad population of patients in the real world. WAYFIND-R will aim to achieve high population representativeness by including a broad patient population with solid tumors in those who are often underrepresented in clinical trials (eg, elderly and frail patients) and a large number of patients across numerous geographic regions. Thus, WAYFIND-R aims to capture inherent population heterogeneity and reflect real-world conditions. WAYFIND-R will also open inclusion criteria to any type of validated NGS-based test of any panel size (eg, from hotspot testing to comprehensive genomic profiling to whole-genome sequencing). This will enable the generating of different levels of genomic data, from a single-nucleotide polymorphism to a whole genome. WAYFIND-R

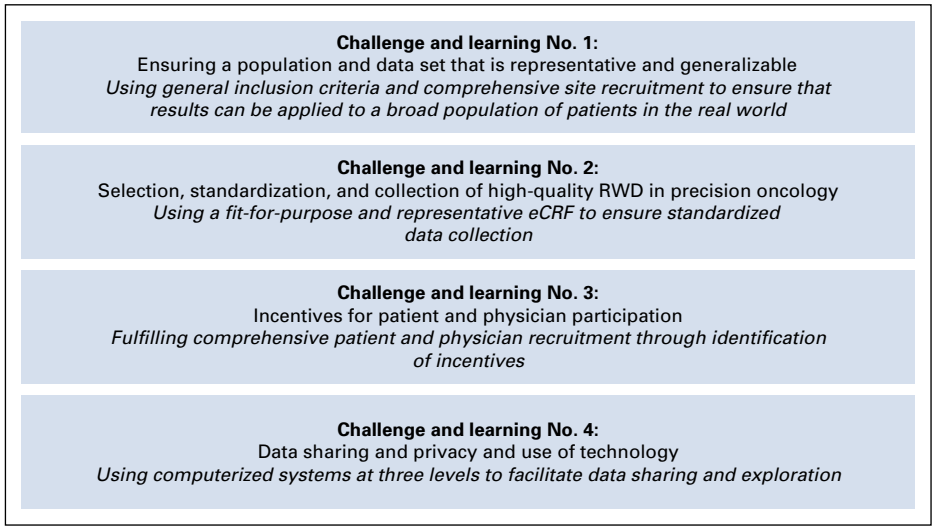

FIG 2. Key challenges and learnings from WAYFIND-R. eCRF, electronic case report form; RWD, real-world data.

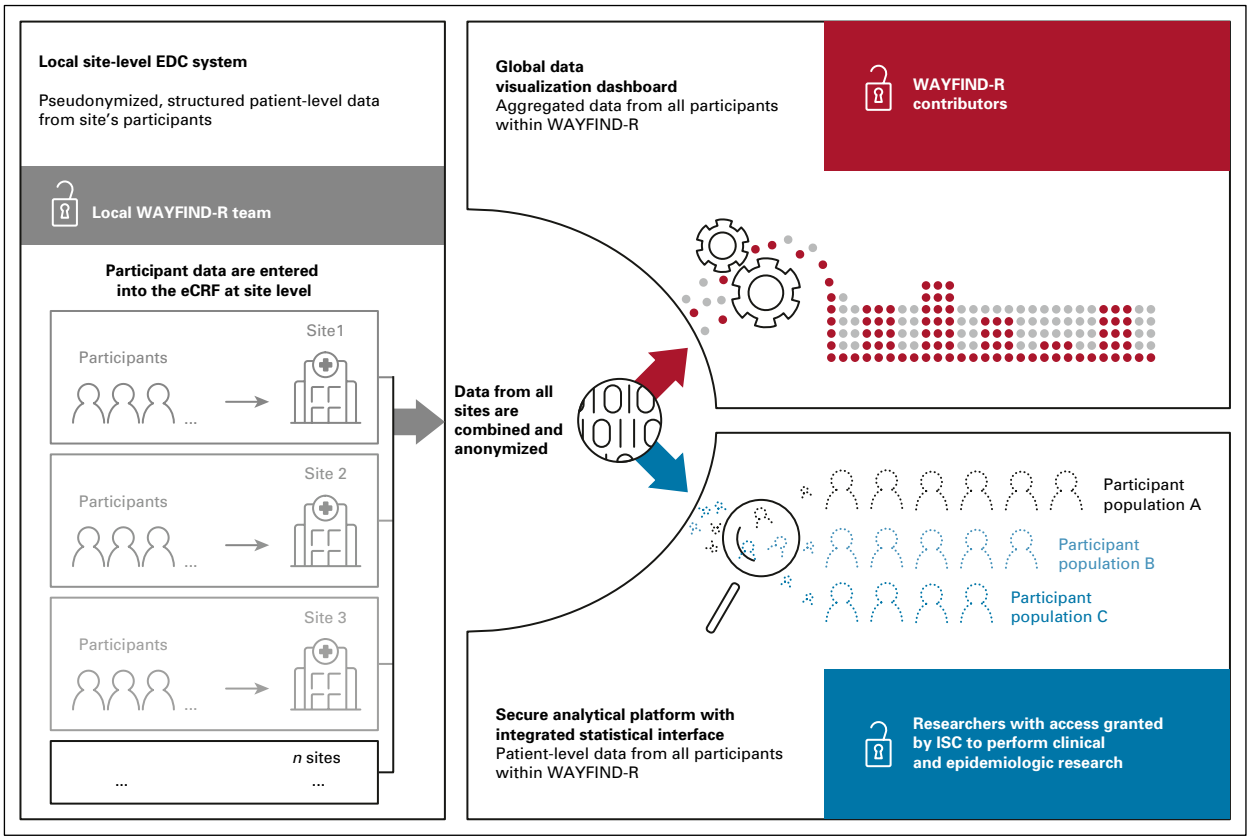

FIG 3. WAYFIND-R data sharing and access framework. A signed and dated informed consent form is obtained from patients. eCRF, electronic case report form; EDC, electronic data capture; ISC, independent scientific committee.

will collect information such as gene name, nature of alteration, DNA/RNA change, protein change, and the alteration itself. Additional omics can also be entered into WAYFIND-R if available, including reportable results from immunohistochemistry, in situ hybridization, proteomics, RNA expression, and epigenomics.

However, intersite variability in specifications of such a broad spectrum of NGS tests leads to challenges when pooling results across clinical sites and interpreting patient outcomes because of an increased likelihood of diagnosis misclassification (eg, when searching for pertinent, wild-type cases of fusion events across NGS assays). To address this, WAYFIND-R will document key information regarding the NGS test (such as details of laboratory certifications, NGS test specifications, biosampling, and results) to ensure optimal usability of the data and trustworthy evidence. In the future, more direct means to collect NGS test results will be explored to ease data collection burden and increase overall data quality.

To enhance population representativeness further, sites will include academic centers, community hospitals, and private clinics with oncology departments in countries across the globe. Such diversity and heterogeneity will improve understanding of health care processes in precision oncology, thereby allowing for analysis of intercountry differences in NGS-tested patient populations, molecular epidemiology, and treatments received.

Challenge and Learning No. 2: Selection, Standardization, and Collection of High-Quality RWD in Precision Oncology

Data quality depends on the consistency, completeness, accuracy, and timeliness of the data, all of which can be heavily dependent on the data source.[15,40] Intersite heterogeneity at the national and local levels can lead to differences in the use of classification or coding systems and timing, as well as completeness of clinical measures. This may lead to challenges associated with collecting standardized data. eCRFs will be used in WAYFIND-R to allow for standardization of data collection at every site. Developing an eCRF that is fit for purpose and representative of various health care systems globally is challenging and associated with difficulties with design consistency, ensuring collection of precise and valuable data and user-friendliness.[41] WAYFIND-R will, therefore, use a customized, flexible, and easy-to-complete eCRF that allows data capture throughout the entire patient journey, from disease diagnosis to resolution or death. The interactive, rules-based, and pragmatic WAYFIND-R eCRF favors drop-down menus,

limits free-text entry, and is based on common data models such as the Anatomical Therapeutic Chemical coding system for treatments,[42] the International Classification of Diseases for Oncology (ICD-O-3 third edition)[43] for diseases, and the Human Genome Variation Society for genomic results. Thus, all data variables collected will comply with FAIR (findable, accessible, interoperable, and reusable) principles, will be harmonized according to global data standards, terminologies, and models, and will allow for pooling from disparate resources, to produce meaningfully comparable and reproducible results.[44]

eCRFs provide opportunities to collect data not available in other sources of RWD (eg, electronic medical records) that are essential in demonstrating the global value of personalized health care (eg, detailed information regarding patient characteristics such as cancer risk factors, sociodemographic status, and NGS test results). In addition, the adverse events collected will include those that have a direct clinical consequence for the administered therapies, patients, or occurrence of pregnancies. Furthermore, collection of RWD from eCRFs allows for the structured acquisition of other data variables not normally captured in clinical trials because they typically focus on one intervention with a standardized diagnostic marker, such as past treatments, post-treatment therapies, and results of MTB discussions.

In the future, WAYFIND-R aims to link data between centers and with other data sources (eg, national cancer registries, prescription databases, claims databases, and mortality registers) via unique or national patient identifications or other methodologies. Overall, linkages will reduce data missingness, enrich the data set with new variables, and increase the panel of research questions that can be answered.

Challenge and Learning No. 3: Incentives for Patient and Physician Participation

The planned comprehensive patient recruitment in WAYFIND-R (ie, approximately 15,000 patients in 5-6 years) may be difficult to fulfill because of the noninterventional nature of WAYFIND-R and challenges associated with identifying incentives to participate. However, to encourage informed patient participation, materials have been cocreated with patient advocates, including a short patient leaflet detailing the ways in which WAYFIND-R could advance precision oncology research. Alongside these advisors, we have identified several incentives for patients to participate in WAYFIND-R: (1) WAYFIND-R will enhance the cancer community's knowledge and thereby advance the field of precision oncology, (2) participation by a site in WAYFIND-R will place it at the forefront of the latest scientific research, and (3) WAYFIND-R will help physicians to define precision oncology treatment plans on the basis of insights from the global dashboard. Although patients may be concerned about privacy, all data gathered will be anonymized and held in a well-organized, secure research database, with strict local privacy regulations and stringent European data protection laws (GDPR) applied. Furthermore, patients who are part of WAYFIND-R are still able to join clinical trials; the data collection within the registry will be paused during the duration of the trial.

Along with patients, we have also identified a number of incentives to encourage participation by physicians. These include (1) the fact that participation allows physicians to join the global WAYFIND-R community and collaborate with peers from other institutions; (2) physicians can gain access to their own local data via the electronic data capture (EDC) interface and the WAYFIND-R global dashboard to provide support with decision-making and fine tuning of a patient's treatment plan; (3) physicians can contribute to a better collection and use of fit-for-purpose RWD; and (4) physicians can conduct their own research, and hospitals can become a learning system for precision oncology (see technologic advances below), fostering clinical trials with innovative therapies.

Challenge and Learning No. 4: Data Sharing and Privacy and Use of Technology

To facilitate data exploration and advance the field of precision oncology, WAYFIND-R will incorporate computerized systems at three levels: (1) a local, site-level data capture system; (2) an online research platform to access the global patient-level data set; and (3) a dashboard showing aggregated data from patients with solid tumors across the globe (Fig 3).

Data entered manually will be collected on the EDC system. Physicians will have access to the data related to patients from their site in a structured format from the EDC platform. This EDC system will allow sites to analyze their own patient-level data in real time, enabling physicians to (1) find similar patients within their institution and discuss possible treatment plans with their colleagues, (2) follow their patients over time and support scientific work at their institution, and (3) attract more clinical trials to their site given the ability to assess local clinicogenomic epidemiology. Such real-time data visualization is not possible in clinical trials because of their blinded nature, and the EDC system will allow better engagement with clinicians and participating sites.

To advance precision oncology and answer scientific questions, researchers willing to analyze the WAYFIND-R global data set will be given access to the anonymized patient-level data hosted in a cloud environment. On the basis of specific access criteria and the scientific merit of the proposal, an independent scientific committee will grant researchers access to this secure analytical platform to perform correlative clinicogenomic analyses using an integrated statistical interface. However, to optimize data sharing while meeting GDPR and local data privacy requirements, the analytical platform will use advanced technology to ensure data privacy by design. As an example, researchers will be allowed to export analysis outputs but not patient-level data, to limit the risk of patient reidentification.

External research partners will have access to a global data visualization dashboard, consisting of aggregated data across all centers globally. The dashboard allows physicians to find a similar patient pool across the whole data set to understand how these patients were treated on the basis of their individual NGS results, thus providing insights to inform clinical treatment decision-making.

WAYFIND-R is also a platform aiming to assess new technologies. It is hoped that technologic advances will allow for future, similar initiatives to incorporate elements such as automatic transfer of electronic medical records into the registry, natural language processing, and ingestion of genomic files that contain information related to all clinically relevant variants and variants of unknown significance. Incorporation of these technologies into WAYFIND-R also will aid its own evolution, helping to reduce the burden of data collection and improve data quality.

In conclusion, through the learnings described in previous sections, we designed WAYFIND-R, a first-of-its-kind cancer registry that offers a global and collaborative platform for the standardized collection of data from patients with solid tumors receiving NGS-based therapies.

A progression of current initiatives, WAYFIND-R will help physicians discuss possible patient treatment plans with their colleagues, improve understanding of the impact of treatment decisions and cancer care processes on health outcomes in these patients, and provide a platform to support the design and conduct of further clinical and epidemiologic research.

WAYFIND-R will also inform on best practice for NGS-based treatment decisions by clinicians, foster global collaborations between cancer centers and thus enable robust conclusions regarding precision oncology outcomes to be drawn, improve understanding of differences in patients' access to advanced diagnostics and therapies, and ultimately drive advances in precision oncology. As RWD are often used in the field of precision oncology for label expansions, post-marketing commitments, and external (synthetic) control arms, the high-quality RWD collected in WAYFIND-R are expected to aid further access to precision oncology in the health care and patient communities by empowering shared decision-making between investigators and the patient community related to research priorities and trial design. The harmonized and standardized EMA-aligned data collection and prospective RWD design of WAYFIND-R enables standards to be defined before data collection and data to be captured from the current standard of care.

To obtain high-quality, generalizable, and comprehensive RWD that can be shared with the research community, improvements in current health care systems are required. These include defining core and clinically meaningful variables to collect; usage, development, and wide acceptance of common data models applicable in oncology; establishing guidelines or policies to incentivize stakeholders to share data; and increasing understanding of the potential value of high-quality, real-world data sets to encourage health care systems to collect data more holistically.

With these learnings, we invite additional stakeholders to join the WAYFIND-R initiative, including patient advocates, policy makers, and national/global cancer societies, to advance precision oncology in the community setting, outside test-driven academic environments.

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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REFERENCES

1. Malone ER, Oliva M, Sabatini PJB, et al: Molecular profiling for precision cancer therapies. Genome Med 12:8, 2020
2. Priestley P, Baber J, Lolkema MP, et al: Pan-cancer whole-genome analyses of metastatic solid tumours. Nature 575:210-216, 2019
3. Flaherty KT, Gray RJ, Chen AP, et al: Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National cancer institute molecular analysis for therapy choice (NCI-MATCH). J Clin Oncol 38:3883-3894, 2020
4. Dienstmann R, Garralda E, Aguilar S, et al: Evolving landscape of molecular prescreening strategies for oncology early clinical trials. JCO Precis Oncol 10.1200/PO.19.00398, 2020
5. Augustine EF, Adams HR, Mink JW: Clinical trials in rare disease: Challenges and opportunities. J Child Neurol 28:1142-1150, 2013
6. Unger JM, Vaidya R, Hershman DL, et al: Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst 111:245-255, 2019

7. Kennedy-Martin T, Curtis S, Faries D, et al: A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 16:495, 2015
8. Dickson D, Johnson J, Bergan R, et al: The master observational trial: A new class of master protocol to advance precision medicine. Cell 180:9-14, 2020
9. Aldrighetti CM, Niemierko A, Van Allen E, et al: Racial and ethnic disparities among participants in precision oncology clinical studies. JAMA Netw Open 4:e2133205, 2021
10. Ginsburg GS, Phillips KA: Precision medicine: From science to value. Health Aff (Millwood) 37:694-701, 2018
11. Mateo J, Chakravarty D, Dienstmann R, et al: A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 29:1895-1902, 2018
12. Moreira A, Masliah-Planchon J, Callens C, et al: Efficacy of molecularly targeted agents given in the randomised trial SHIVA01 according to the ESMO Scale for clinical actionability of molecular targets. Eur J Cancer 121:202-209, 2019
13. Luchini C, Lawlor RT, Milella M, et al: Molecular tumor boards in clinical practice. Trends Cancer 6:738-744, 2020
14. Merck Sharp & Dohme Corp: KEYTRUDA® (Pembrolizumab). Prescribing Information, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s110lbl.pdf
15. Booth CM, Karim S, Mackillop WJ: Real-world data: Towards achieving the achievable in cancer care. Nat Rev Clin Oncol 16:312-325, 2019
16. Massard C, Michiels S, Ferté C, et al: High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: Results of the MOSCATO 01 trial. Cancer Discov 7:586-595, 2017
17. Rodon J, Soria JC, Berger R, et al: Genomic and transcriptomic profiling expands precision cancer medicine: The WINTHER trial. Nat Med 25:751-758, 2019
18. Sicklick JK, Kato S, Okamura R, et al: Molecular profiling of cancer patients enables personalized combination therapy: The I-PREDICT study. Nat Med 25:744-750, 2019
19. Cave A, Kurz X, Arlett P: Real-world data for regulatory decision making: Challenges and possible solutions for Europe. Clin Pharmacol Ther 106:36-39, 2019
20. US Food and Drug Administration (FDA): Framework for FDA's Real World Evidence Program, 2018. https://www.fda.gov/media/120060/download
21. Lewis JRR, Kerridge I, Lipworth W: Use of real-world data for the research, development, and evaluation of oncology precision medicines. JCO Precis Oncol 1: 10.1200/PO.17.00157, 2017
22. Parab TM, DeRogatis MJ, Boaz AM, et al: Gastrointestinal stromal tumors: A comprehensive review. J Gastrointest Oncol 10:144-154, 2019
23. Call JW, Wang Y, Montoya D, et al: Survival in advanced GIST has improved over time and correlates with increased access to post-imatinib tyrosine kinase inhibitors: Results from Life Raft Group Registry. Clin Sarcoma Res 9:4, 2019
24. Sánchez-Cousido LF, Piedra MR, Flores ML, et al: P2.16-43 Immunotherapy in elderlies. Real world data. J Thorac Oncol 14:S882-S883, 2019
25. Goossens-Laan CA, Kil PJ, Bosch JL, et al: Patient-reported outcomes for patients undergoing radical cystectomy: A prospective case-control study. Support Care Cancer 22:189-200, 2014
26. Blonde L, Khunti K, Harris SB, et al: Interpretation and impact of real-world clinical data for the practicing clinician. Adv Ther 35:1763-1774, 2018
27. Khosla S, White R, Medina J, et al: Real world evidence (RWE)—A disruptive innovation or the quiet evolution of medical evidence generation? F1000Res 7:111, 2018
28. Wedam S, Fashoyin-Aje L, Bloomquist E, et al: FDA approval summary: Palbociclib for male patients with metastatic breast cancer. Clin Cancer Res 26:1208-1212, 2020
29. Drilon A, Siena S, Dziadziuszko R, et al: Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: Integrated analysis of three phase 1-2 trials. Lancet Oncol 21:261-270, 2020
30. US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER): Review of Study Report No WO40977: Comparative Analysis of ROS1-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer between Patients Treated in Entrectinib Trials and Crizotinib Treated Patients From Real World Data, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%202127260rig1s0000therR.pdf
31. Rubinstein SM, Warner JL: CancerLinQ: Origins, implementation, and future directions. JCO Clin Cancer Inform 10.1200/CCI.17.00060, 2018
32. Marinis F, Wu YL, de Castro G Jr, et al: ASTRIS: A global real-world study of osimertinib in >3000 patients with EGFR T790M positive non-small-cell lung cancer. Future Oncol 15:3003-3014, 2019
33. European Medicines Agency (EMA): Patient Registries. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries
34. AACR Project GENIE Consortium: AACR Project GENIE: Powering precision medicine through an international consortium. Cancer Discov 7:818-831, 2017
35. Mahal BA, Alshalalfa M, Kensler KH, et al: Racial differences in genomic profiling of prostate cancer. N Engl J Med 383:1083-1085, 2020
36. Kamran SC, Xie J, Cheung ATM, et al: Tumor mutations across racial groups in a real-world data registry. JCO Precis Oncol 10.1200/PO.21.00340, 2021
37. Schumacher FR, Basourakos SP, Lewicki PJ, et al: Race and genetic alterations in prostate cancer. JCO Precis Oncol 10.1200/PO.21.00324, 2021
38. Green ED, Gunter C, Biesecker LG, et al: Strategic vision for improving human health at the forefront of genomics. Nature 586:683-692, 2020
39. D'Agostino M, Waage A, Lahuerta J-J, et al: Validation and improvement opportunities of the revised international staging system for multiple myeloma: An analysis on mature data from European clinical trials within the harmony big data platform. Blood 134, 2019 (abstr 1773)
40. European Medicines Agency (EMA), Committee for Human Medicinal Products (CHMP): Guideline on Registry-Based Studies, 2021. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf. 22 October 2021. EMA/426390/2021
41. Bellary S, Krishnankutty B, Latha MS: Basics of case report form designing in clinical research. Perspect Clin Res 5:159-166, 2014
42. World Health Organization Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health (NIPH): 2022: Guidelines for ATC Classification and DDD Assignment, 2022. https://www.whocc.no/filearchive/publications/2022_guidelines_web.pdf
43. World Health Organization (WHO): International Classification of Diseases for Oncology (ICD-O) (ed 3, revision 1), 2013. https://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf
44. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al: The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 3:160018, 2016