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The Master Observational Trial: A New Class of Master Protocol to Advance Precision Medicine

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Summary

This commentary introduces a new clinical trial construct, the Master Observational Trial (MOT), which hybridizes the power of molecularly based master interventional protocols with the breadth of real-world data. The MOT provides a clinical venue to allow molecular medicine to rapidly advance, answers questions that traditional interventional trials generally do not address, and seamlessly integrates with interventional trials in both diagnostic and therapeutic arenas. The result is a more comprehensive data collection ecosystem in precision medicine.

Keywords

Master, protocol, trial, innovation, real-world data, evidence, innovation, quality, ROOT

Introduction

Advances in basic science allow a deeper understanding of the cellular underpinnings of disease. Without clinical correlation, however, many of these molecular techniques take decades to translate into improved patient care. The interplay of genomes, transcriptomes, proteomes, metabolomes, epigenomes, cellular metabolism, microenvironment, immune characteristics, gut biome, and other factors steadily increases the complexity in understanding how everything fits together. One of the largest impediments to the advancing of molecular medicine is the clinical infrastructure to allow exploration, validation, and implementation of the tools needed to turn precision testing into personalized treatment. (Subbiah and Kurzrock, 2018).

Molecularly Based Interventional Trials

The majority of what we know in precision medicine has come from clinical trials centered on specific alterations that directly impact either disease prognosis or treatment decisions. These interventional trials mitigate bias by fixing as many variables as possible, such as selecting patients that meet certain criteria, limiting testing to selected laboratories or methods, defining the threshold of testing results that trigger treatment, limiting treatment to one point in time in the patient journey, and, in some cases, randomization of patients. Biomarker data are integrated into the trial design

and captured as part of the trial. The result is a scientifically stringent glimpse of a specific type of patient at a specific point in time: tested, treated, followed-up, and reported using precise rules. Regulatory agencies, such as the United States Food and Drug Administration (FDA), consider interventional trials tied to defined molecular testing as the gold standard for data collection in precision medicine. These trials advance clinical practice through identification of testing and treatments that can be applied to defined patients.

Master interventional protocols are an important evolution of traditional interventional trials. By using a common testing method, unified protocol, and shared infrastructure, multiple single arm trials tied to specific biomarkers can run in parallel. Arms can be opened and closed as information is gained (Woodcock and LaVange, 2017).

Challenges of Molecularly Based Interventional Trials

Interventional trials are generally sponsored by groups who want to answer specific questions that will allow regulatory bodies to evaluate the benefit of a distinct intervention. One of the most ambitious and comprehensive interventional master protocols in oncology is the National Cancer Institute's Molecular Analysis for Therapy Choice Trial (NCI-MATCH). In a 2017 poster update, NCI-MATCH had screened close to 6,000 patients with 18% of patients harboring an alteration that would allow them to be included in a treatment arm of the protocol. At that reporting, 8 of 30 arms had enrolled the minimum patient number to meet the scientific threshold. Patients in these arms were scattered across all tumor types. Like most other interventional trials, MATCH is focusing on the therapeutic advantage of a treatment in patients with certain biomarker profiles (Harris, L. et. al., 2017). MATCH is extremely valuable to advance precision medicine but has not been designed to provide comprehensive answers. In addition, it is unclear how a typical trial patient would compare to a patient in the real world (Dear et al., 2017; Kennedy-Martin et al., 2015). Interventional trials usually focus on narrow molecular signatures and only one line of therapy.

Interventional trials are a specific tool for a specific purpose—akin to finding a single piece of a large jigsaw puzzle, where personalized medicine represents the entire completed puzzle. Ideally, if we could run enough interventional trials and integrate all data into one source, we could eventually piece together a comprehensive understanding of personalized care. However, due to cost, complexity, market forces, and other factors, it is extremely unlikely that we will ever build a comprehensive model of any disease using interventional trials alone.

Real-world Data (RWD) with Molecular Annotation

Real-world data can be defined as any information to help advance patient care that comes from sources other than traditional clinical trials. Sources may include electronic medical records, mobile devices, insurance claims, and disease registries. Analysis of this data generates real-world evidence that, in turn, can generate meaningful insights into unmet needs, interventional pathways, and the clinical and economic impact on patients and healthcare systems. The FDA has recognized that RWD of sufficient quality may provide a better snapshot of how an intervention impacts a broader patient population. The hope is that RWD, because of its plentiful nature, can be used to fill knowledge gaps that exist between limited number of patients in clinical trial scenarios and the vast number of patients in the actual practice of medicine (Booth and Tannock, 2014; Sherman et al., 2016). The FDA evaluates the quality of RWD on the basis of how well the data collection effort negates bias.

RWD is most commonly obtained retrospectively from electronic health records (EHR), charts, and claims information. Focused efforts, such as retrospective observational trials, can improve data collection reliability. These efforts generally limit their purview to defined sets of patients with a certain biomarker signature at a specified time point.

Prospective observational trials employ many of the same methods as interventional trials to mitigate bias. Some of these include written protocols, screened patient populations (although, generally not to the degree of an interventional trial), prescribed testing (although, often not limited to one specific method), standardized reporting, consistent reassessment intervals, and unified training. Molecular testing data that are collected from these studies often focus on a limited number of biomarkers with the results of different laboratories being lumped together. Frequently, only a certain point of time in the treatment is collected.

Challenges of Molecularly Based RWD

Most RWD is collected retrospectively. Data from these sources is frequently non-standardized, incomplete, inconsistent, non-accessible, siloed, and may still harbor biases that are not ameliorated by large sample size (Berger et al., 2016; Kaplan et al., 2014). Complete biomarker data is usually not present. The heterogeneity of both inter-physician and intra-physician care can introduce bias even when a formal retrospective analysis identifies a pre-defined outcome in the reviewed records. The notations in the electronic medical records may be confusing, contradictory, incomplete, and/or difficult to interpret.

Adding molecular annotation to retrospective RWD, especially in oncology, creates additional complexity in areas such as:

1) Equivalence: The equivalence between different testing methods for the same biomarkers is largely unknown. There may be analytical differences even with similar methods on similar specimens and/or a lack of clinical data identifying best practices (if any) of one testing type or testing tissue as compared to another. (Aggarwal et al., 2018; Stetson et al., 2019).
2) Interpretation: The complexity of molecular analysis and its clinical application has created significant variability in testing and reporting. To try to limit this variability, professional societies continue to issue guidance, but these recommendations usually are in response to gaining experience with the test and a body of information from which recommendations can take place. For example, testing for the human epidermal growth factor receptor-2 (HER2) in breast cancer was initially approved along with the drug trastuzumab in 1998, and yet the last major update on the best methods to test for HER2 was updated in 2013. (Wolff et al., 2013). Further, we are still in the early stages of understanding how to use powerful new technologies such as next-generation sequencing. (Jennings et al., 2017; Roy et al., 2018). On the clinical side, identical biomarker profiles can be interpreted differently by different physicians, leading to different treatment even with the same findings. (Rieke et al., 2018).
3) Recording: The source of much biomarker data in RWD comes through reports in the medical record. Frequently, molecular testing is performed in outside laboratories independent of the ordering physician. Results of this testing are often entered into the electronic health record in analog format (i.e., paper document scanned into record or PDF). Unless a research group has direct access to digital formats of laboratory results and clinical data, molecularly annotated RWD from the EHR is not easily captured. In addition, when results are included in clinical records, they are often qualitatively summarized as being

positive or negative without discussing details such as testing method, laboratory, or any crucial quantitative information.

The Evidentiary Gap in Personalized Medicine

Unraveling the molecular conundrum of disease requires a more comprehensive understanding of smaller subsets of patients segregated by cellular processes, and a fuller understanding of how these subsets relate to each other. This quest requires several principles to come together:

1) Precise classification of broad molecular signatures;
2) Standardized clinical elements longitudinally tied to molecular data;
3) Sufficient quantity of quality data to allow scientific comparison between groups;
4) The ability to analyze and review complex datasets; and,
5) The mechanism to evolve interventions as new information is learned.

The evidentiary gap in precision medicine lies between the data from the narrowly focused low-quantity, high-quality interventional studies and lower-quality but plentiful RWD. At the current time, neither interventional data nor RWD can fulfill the five criteria listed above.

The Master Observational Trial (MOT) as a Solution

In order to fill the gap that exists in data collection in precision medicine and fulfill the requirements for a comprehensive strategy, we propose a new class of clinical master protocol: the Master Observational Trial. The MOT is an amalgamation of master interventional trials, prospective observational trials, and a precise method of cataloging molecular data (the Molecular Matrix) (see **Figure 1A**).

The General Structure of an MOT

The MOT is a prospective, observational trial that broadly accepts patients independent of biomarker signature and collects comprehensive data on each.
MOTs will likely have the following common characteristics:

1) **Transparent governance.** Multi-institutional and international efforts are essential in the designing and implementing of an MOT. Leadership must transparently address cross-institutional and cross-stakeholder concerns to bring groups together, especially across borders where practice settings and data collection regulations are different.
2) **Centralized trial administrative functions.** These provide organizational consistency across institutions and include central leadership, contracting, institutional review board (IRB), training and certification, and audit.
3) **Traditional interventional trial organization.** This helps mitigate bias by standardizing as much as possible and includes a written and registered protocol, standardized case-report forms, defined reporting, and regular queries for missing or unclear data.
4) **IRB approved patient consent and HIPAA (or equivalent) privacy authorization.** These important elements of the MOT are developed country by country to comply with data privacy regulations, allow for deeper data collection on certain patients in order to answer specific questions, and allow access to archived tissue specimens to perform additional biomarker testing.
5) **Precise molecular testing classification.** Biomarkers, both present and absent, are recorded along with temporal association with treatment, tissue location, testing laboratory, testing details, and test version (see **Figure 1A and 1B**). This allows for the grouping of patients who

have received similar testing and can help determine results that may otherwise be less certain due to various factors. Newer testing techniques can be easily introduced to identify benefit.

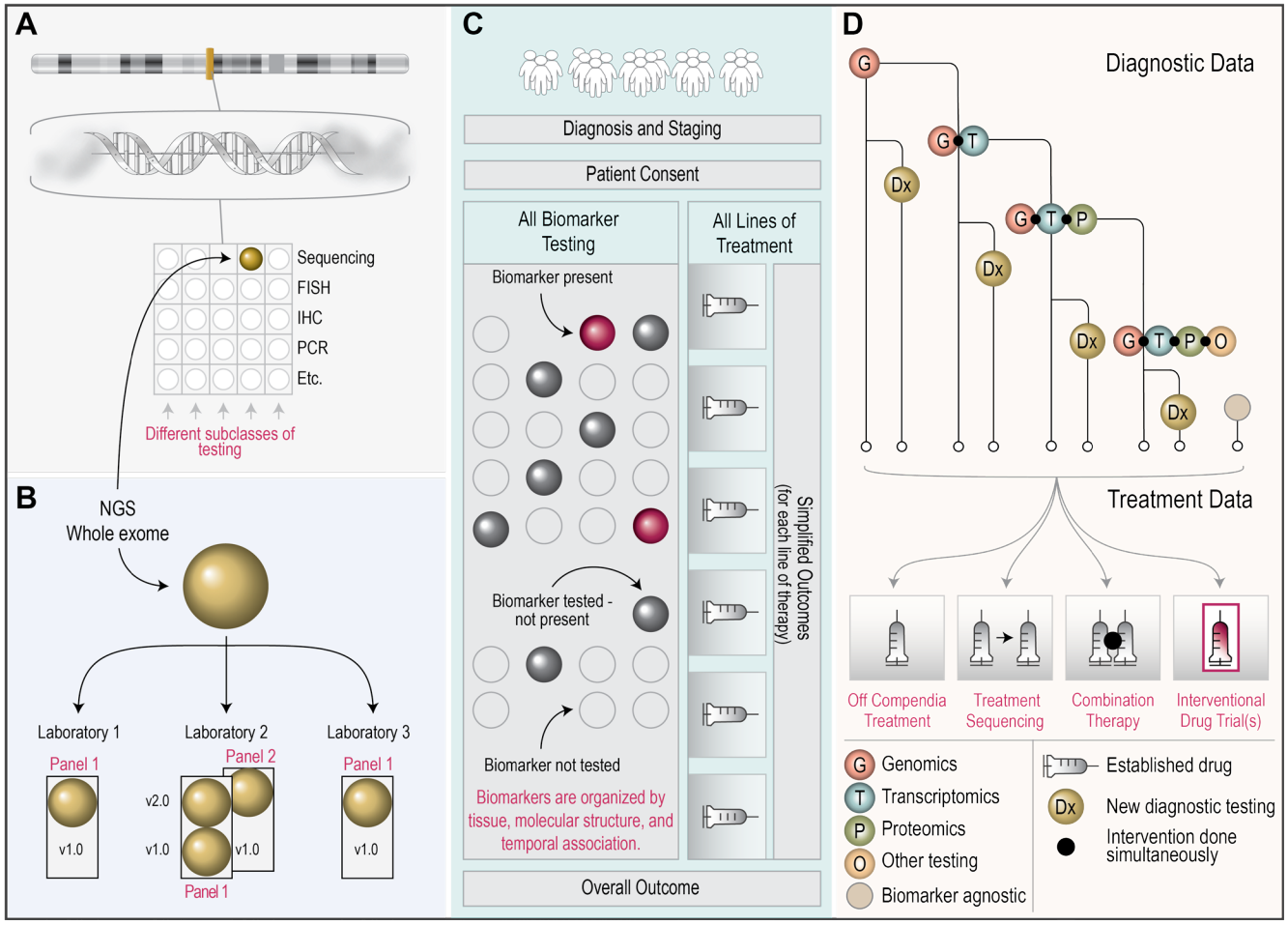

Figure 1. The Master Observational Trial (MOT)

(A) **The Molecular Classification Matrix.** This is a graphical representation of the manner that the MOT classifies biomarker testing (this example examines a specific region of DNA). Testing methods are broken into technology (rows) and then are further subdivided into the general method that the given technology is applied (columns).
(B) **Laboratory test details: versions and tissue origin.** Biomarker testing is initially categorized using the Molecular Classification Matrix (**Figure 1A**). Each specific technology and method (e.g., next-generation sequencing or NGS) is further broken down into a subcategory (i.e., whole exome sequencing), and then laboratories are grouped by those using similar analysis instrumentation and techniques on similar tissue. Versions of tests are also collected to allow for distinction between evolving technology.
(C) **Master Observational Trial Overview.** This shows the structure of the MOT. Patients are broadly accepted into the trial along with diagnosis and staging (disease extent) information and informed consent. Biomarker testing results (both positive and negative) are collected and classified using methods shown in **Figures 1A** and **1B**. High level outcomes are collected in connection with each line of therapy. All the information is tied together in a prospective observational registry using standardized reporting methods and metrics.
(D) **Interconnectivity and modularity of MOT design.** All data collected is sorted and organized to allow for comparison and analysis of any testing or treatment method in combination or series. The evolution of data collected in the MOT starts with genomic (and other -omic) data, and then, as technology and availability progress, additional molecular testing methods are included. Novel molecular testing can be introduced, creating different arms (diagnostic modules). All diagnostic data is tied to treatments both standard and those not part of established compendia, combination therapies, or sequenced therapies (therapeutic modules). The prospective nature and precise molecular characterization allow for identification of specific subgroups of patients who can participate in interventional clinical trials that are directly related to or external to the MOT.
Abbreviations: FISH – fluorescent in situ hybridization; IHC – immunohistochemistry; PCR – polymerase chain reaction.

6) **Standardized clinical data elements.** The broad collection of data across multiple lines of therapy needs to have at least essential core data elements collected. Core elements need to

be robust enough to answer multiple questions and are likely going to be substantially different for different fields of medicine (see **Figure 1C**).

7) **Longitudinal data collection**. By collecting key information on each phase of a patient's journey from diagnosis to disease resolution or death, broader understanding of complex interactions can be explored. This longitudinal approach is necessary to give real-world context to knowledge gained from traditional trial data.
8) **Modular trial design (internal to protocol).** Although data is observational, there needs to be a broad understanding of what types of patients should be included in the trial. This may be through focusing on certain types of testing or classes of treatments (see **Figure 1D**).
9) **Seamless integration with interventional trials or RWD (external to protocol).** Attaching interventional trials, including single arm, master protocol, or randomized trials, inside the MOT structure allows for the answering of specific questions about new testing or therapy. This data can be directly integrated with the broad data collection that takes place within the MOT. Separate trials will have separate protocols, IRB approval, patient consent, and other components as necessary to be integrated into the MOT (see **Figure 1D**).
10) **Artificial intelligence and machine learning from multiple perspectives**. MOTs will collect massive amounts of data. Artificial intelligence and advanced computing will be essential in turning raw data into actionable hypotheses. The higher quality and accessibility of the structured data in an MOT will provide improvement in adaptive algorithm development. Confirmation of findings through shared data access is valuable to remove potential bias.

The Master Registry of Oncology Outcomes Associated with Testing and Treatment (ROOT)

Within every trial type there is flexibility in design and implementation. MOTs are not any different. Areas that are likely going to see emphasis surround data collection needs, quality improvement, and/or broadening participation. The recently announced ROOT trial in oncology is one of the first examples of an MOT. Some of the modifications in general design and implementation that may or may not be present in other trials are as follows:

1) **Staged approach.** MOTs are complex entities with many moving parts and competing interests. Rather than solve every complex problem that could be faced initially, ROOT started by focusing on two areas: 1) the unmet need of quality data to bridge the gap between clinical trials and unstructured RWD and 2) how this data could be collected using existing infrastructure. A core group of clinical leaders and cornerstone institutions agreed to work together to identify obstacles, propose solutions, and work toward building a national prospective oncology registry that could then advance globally. Several areas of caution were identified early on. These included concern for data collection for research purposes without IRB approval and patient consent, cumbersome collection methods, increased physician work, financial constraints, data sequestration, and data governance. An IRB-approved clinical protocol was developed alongside with general business framework, and cornerstone groups formally agreed to work together to find equitable solutions to the complex issues that would arise as the MOT evolved.
2) **Standardized clinical data elements.** ROOT uses a slight modification of the core data elements tied to molecular data published through a multi-stakeholder effort (Conley et al., 2017). The simpler data elements allow focused data collection of the most impactful data points on broader patient populations.

3) **Data collection as part of current clinical flow**. Data collection methods and forms mesh to current clinic personnel and physician workflow, thus minimizing impact on clinics, especially physician time.
4) **Shared data collection and protected physician time.** Non-physician staff report data recorded in the medical record (e.g., treatments and dates), and physicians only report outcomes and medical decision making. The physician work has been designed to be part of a regular visit and to add negligibly to the time of that visit. Physician time to enroll patients must be protected in order to allow for broad patient accrual.
5) **Shared data access.** ROOT will allow the scientific communities of participating institutions access to deidentified data placed in a server that will enable hypotheses generation and data review and publication. This broad access allows for greater research in order to help to advance precision medicine. To encourage sharing, institutions that are not contributing data may receive access through data delay, fees, or limited access. This will be determined by the participating institutions.
6) **Shared business models.** To keep costs of operation low, and with the benefit of access of larger patient populations for research and clinical trials, data providers are asked to receive less than fair market value for collecting the elements that are required by the MOT. Then, as data is collected, if any commercial group wants access to the provided data for research purposes, net revenue (if any) will be shared by the institutions based on quantity and quality of provided data to allow continued participation.

Discussion

Challenges

Broad physician support and patient numbers. MOTs can fill the gap that currently exists in precision medicine but only to the degree that these are supported by community and academic practices, both nationally and internationally. Areas of complexity that could hinder participation include data sharing, publication rights, intellectual property, financing and governance. Finding the right models that lead to formal contracts and allow for unification across institutions and borders could be challenging. Encouraging clinicians to report data when they are already busy could also create barriers. The use of physician extenders or trained coordinators can facilitate this process.
Financing. The data in MOTs can benefit patients, physicians, biopharmaceutical companies, laboratories, manufacturers, payers, and regulators. Widespread support from groups who will receive benefit are needed to finance MOTs. The ambitious nature of the MOT may keep groups on the sidelines waiting to see traction before providing support. This could be ameliorated by providing early adopters quicker access to data than those who provide support later.
Molecular data sharing. Laboratory data has many layers of information that could be used to help better understand precision medicine. Due to technological, competitive, and financial barriers, many groups have been reticent to provide data to outside groups.
Sustainability. Turning precision medicine into personalized care is an ongoing effort. New technology and possible treatments are advancing faster than we are collecting the data to understand how to use these tools. We need long-term efforts to answer these questions. MOTs, like all other data collection efforts, need long-term support for success.
Regulatory adoption. The FDA has used non-interventional data to support limited actions, but generally will not use RWD in regulatory decisions. The added quality of the MOT will likely increase the confidence to use RWD in some approvals.

Opportunities

Precision medicine is complicated. No one group has the patient numbers and resources to collect the data necessary to fully advance the field. We need accessible, quality data on hundreds of thousands of patients, harboring the breadth of molecular alterations in order to develop scientifically rigorous analysis. Much of current retrospective RWD efforts are not of high enough quality to answer the complexity of questions. Interventional trials are time consuming and costly. Ultimately, the MOT provides a new vehicle to harness the power of RWD in order to unlock personalized medicine. It provides heretofore unavailable opportunities to yield information that has widespread benefits to patients, families, clinicians, regulators, payers, industry, researchers, and society.

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Declaration of Interests

DD: Stock and Other Equity Interests (Cofounder, CEO, and shareholder of Taproot Health who is the sponsor of ROOT); Speaker's Fee (Novartis).
JJ: Consulting or Advisory Role (Foundation Medicine).
RB: Stock and Other Equity Interests (Co-owner of Third Coast Therapeutics, which has an option to license patents on which he is an inventor, and which relate to experimental drugs for the treatment of cancer.).
RO: Stock and Other Equity Interests (Cofounder, CCO, and shareholder of Taproot Health who is the sponsor of ROOT).
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RK: Stock and Other Equity Interests; (IDbyDNA, CureMatch, Inc., and Soluventis); Consulting or Advisory Role (Gaido, LOXO, X-Biotech, Actuate Therapeutics, Roche, NeoMed, Soluventis, and Pfizer); Speaker's Fee (Roche); Research Funding (Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, Konica Minolta, DeBiopharm, Boerhringer Ingelheim, and OmniSeq [All institutional]); Board Member (CureMatch, Inc).
JJ, RB, RK, SS are principal investigators of the ROOT trial. These are uncompensated, volunteer roles.

Author Contributions

Conceptualization, DD; Methodology, DD, JJ, RB, RK, RO, VS; Writing-Original Draft, DD; Writing-Review & Editing, DD, JJ, RB, RK, RO, VS; Supervision, JJ, RB, RK, VS.

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