The Molecular Evidence Development Consortium (MED-C) a Shared Method to Advance Personalized Medicine

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Abstract:

The molecular understanding of disease and associated treatment is becoming a reality due to rapid advances in science. Yet, the high cost of clinical trials and diversity of diseases make collection of molecular outcomes through traditional means difficult for anything but the most common mutations. Furthermore, few physicians are trained in personalized medicine and many patients do not have access to these promising advancements. In order to address these obstacles we propose the development of the Molecular Evidence Development Consortium (MED-C). This organization uses existing infrastructure to introduce molecular testing to patients, and also increase numbers of patients for established clinical trials, and where trials do not exist, access to advanced testing and promising treatments as part of an iterative, prospective observational registry (SOR). Patients meeting simplified inclusion will be tested using standardized means and then based on mutation profile will be offered centrally determined treatment options from which the physician and patient can choose. If there is an option that includes a targeted drug it could be provided to the patient in an IND-exempt clinical trial or through participation in an IND clinical trial with already marketed, non-compendia drugs or new compounds. The treating physician will have facilitated access to testing and treatment pathways, and will provide de-identified simplified outcome data to the registry. The stakeholders include payors, pharma, lab industry, patient groups, physicians and regulatory bodies. Each derives a net benefit of participating in the endeavor.

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Background

With the rapid advancement of molecular biology and the logarithmic decrease in cost of sequencing, we sit on the cusp of the promise of personalized approaches in every arena of medicine.

The aims of personalized medicine are well understood: avoiding ineffective treatment, decreased costs, improved outcomes, better ability to predict prognosis, etc. The goals of patients, providers and payors align in developing this dream. In addition, other groups such as laboratories and pharmaceutical companies see the realm of personalized medicine as an area of innovation and opportunity.

There are challenges in unlocking molecular medicine. The complexity of biomarkers and the often-large numbers of individuals needed for screening makes randomized trials difficult. Without larger number of patients to study, randomized controlled trials are likely for only the most common marker types. The clinical impact of less frequent variants will likely take decades (if ever) to be fully understood. In addition to the scientific hurdles, budgetary tightening and increasing cost of care create additional problems.

The Molecular Evidence Development Consortium (MED-C)

(MED-C) is an amalgamation of stakeholders. Using combined efforts and existing infrastructure; together they create a robust standardized outcome registry (SOR). The MED-C SOR differs from traditional observational registries due a high degree of standardization inside the registry. Standards include: patient characteristics, testing methodology, treatment pathways, outcomes reporting (both physician and patient) and toxicities. An independent oversight body uses the information gathered to allow iterative learning and refining of testing and treatment pathways. The hope is to unlock the complexity of personalized medicine in a stepwise fashion. The MED-C SOR compliments current and future clinical trials.

MED-C Stakeholders (See Figure 1)

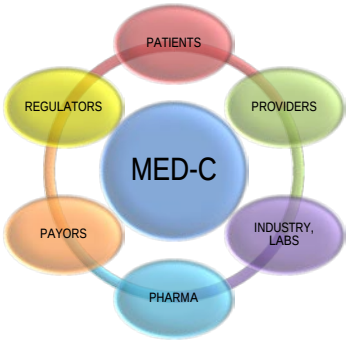

Figure 1: MED-C Stakeholders

The following groups form MED-C:

Patients (and Patient Advocates): Patients will agree to participate in the MED-C SOR and to undergo standardized molecular testing and comply with defined, standard of care treatment protocols. Patients further agree to collection of de-identified data by their physicians (e.g. cancer: diagnosis, stage, treatment history, mutation status and progression free survival, overall survival, severe toxicities, etc.) and archived in the MED-C Data Repository (see below). The registry will also develop data entry tools to enable patients to report outcome measures including QOL and toxicity. In addition, patients will be asked if they would allow further exploration of their data in specific cases of scientific research in specific biomarker subtypes.

Physicians: Participating physicians will enroll patients who meet defined criteria and who agree to share data in the MED-C registry. The physicians are required to follow defined protocols for testing and treatment options (all standard of care) and report defined outcomes for each patient. In addition they will report severe adverse events or deaths of registered patients.

Payors: Payors agree to cover the defined testing and routine care of the patient as long as the labs agree to report the results of the biomarkers to the SOR. As able, new technology will replace old technology to improve patient care and yet not dramatically increase cost. Payors will require patient and provider participation in the registry and in turn will have access to the registry data.

Pharma: Pharmaceutical companies will support investigator instigated IND-exempt or IND-originated trials, or sponsor phase II single arm IND-trials to patients with defined mutations identified in the SOR. Clinical results of the treatment protocols (including comparison to internal controls of patients with biomarkers not treated) will be published on a regular basis. These outcomes will integrate with other research and assist in hypothesis generation and regulatory approval. This data will include real-time toxicity data.

Laboratories and Testing: Laboratories meeting the high-quality testing standard (based on results not on platforms) required by MED-C will perform analysis as defined by protocols. The testing standard will be compared to existing standards (such as companion diagnostics) and will be established as a new standard that can be used as a comparator for other new technologies

Regulators: Regulators will provide input to the general organization, principles and methods of MED-C. They provide key opinions on treatment protocols and data collection elements and ensure MED-C continues to develop and improve data collection to assist in regulatory approval and coverage decisions.

MED-C Organization (see Figure 2)

MED-C Non-Profit Corporation (MED-C.org): is a 501(c)(3) public charity dedicated to the advancement of personalized medicine in all areas independent of subspecialty. MED-C.org handles all aspects and development of MED-C projects and databases. This entity reports to the MED-C Board (see below). Specific activities include the development of infrastructure, building relationships between stakeholders and developing proposals. The infrastructure and methods that are developed by MED-C will be re-used in other disease states and subspecialty areas.

MED-C Board of Directors (MED-C Board): The Board serves as an independent body to align interests amongst all stakeholders and to avoid any concerns for conflict of interest. This group will be expanded as needed to keep robust and balanced leadership of the organization.

MED-C Executive Advisory Committee (MED-C EAC): The MED-C EAC brings representatives from all stakeholder groups together to advise the MED-C Board on the direction of the organization. They may explore items such as new protocols (new testing or new treatment), expansion of projects into

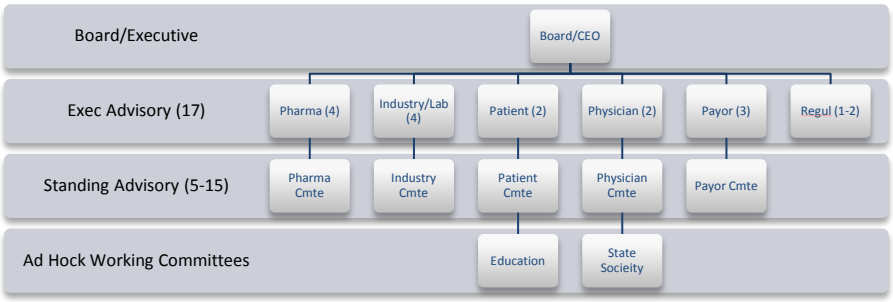

Figure 2: MED-C Organization and Example of Advisory Panels

different disease states, evolution of research methods, better methods of working together, etc. The MED-C Board in connection with the CEO invites individuals to sit on the EAC. Individuals chosen will usually have been serving on a MED-C Advisory Committee (MED-C AC see below) and have shown commitment to advancing personalized medicine. This committee can be expanded or contracted as is needed to meet needs. It will seek to have representation from all stakeholders to keep the consortium well represented in all areas. The number of this committee is determined by the board, but will likely be around 17 individuals.

MED-C Advisory Committees (MED-C AC): The AC is made up of industry specific groups. These committees will discuss broad concerns and direction that MED-C could help solve. These groups will be generally be represented by members of the EAC to the board. They will also have direct interactions with board members or MED-C executive staff at meetings of the committees. The Board will determine the size and tenure of these committees and succession procedures.

Medical Oversight Committee (MOC): The MOC is an independent group of nationally and internationally recognized thought leaders in the areas of molecular and clinical medicine. They work with MED-C leadership to determine areas of testing and treatment. They develop molecular treatment pathways, provide ongoing review of data from the registry and modify or expand protocols as information is gathered. They agree to oversee the publishing of the results of the registry in a timely fashion.

MED-C Laboratory Oversight Committee (LOC): This group will work with payors, regulators, thought leaders and professional societies to the development of high quality, reproducible laboratory testing standards. Prior to finalizing any standard, they will seek input from established thought leaders such as the College of American Pathologists (CAP), the Association of Molecular Pathologists (AMP) and regulatory groups. The standards will usually be able to direct immediate clinical decisions, but also allows possible consideration for research protocols. The MED-C standard will be the basis for specific protocols. They will work with existing groups wherever possible to verify that labs meet these scientific criteria prior to allowing these labs to participate in the testing.

MED-C Projects: In general, a project (or protocol) will focus in areas where clinical practice has shown a significant improvement in care (such as improved patient outcomes, quality, and/or cost) based on some aspect of molecular medicine. In these areas, often some aspect of molecular medicine will shown to be increasingly important in patient care (i.e. an area where treatment decisions are increasingly made using molecular markers based on clinical utility) but yet not have the robust clinical utility data that is wanted.

Projects will generally start at the Board and the MED-C.org level, but can be proposed from any of the stakeholders for consideration. Occasionally a project could originate from an outside group, but it would still need to receive approval by MED-C leadership. **Figure 3** shows possible example projects, testing methodology and originator (or sponsor). Certain testing may be paid for by payors (MED-C projects) but also could be paid for by pharma or other patient support groups.

MED-C Registry (or SOR): The data from a specific project will be stored in a standardized observational registry (SOR). All data, including mutation profile, inclusion criteria, treatment pathways, outcomes and toxicities (etc.) will be captured in the MED-C SOR in a HIPAA compliant fashion

MED-C Data Repository (Database): All the data from the individual projects are stored in the MED-C Database. This database will generally be open access, although there may an access fee based on commercial or non-commercial research.

Every effort will be made to correlate the MED-C database with outside sources such as claims, tumor registries, patient advocacy efforts, etc. The goal is a robust database of

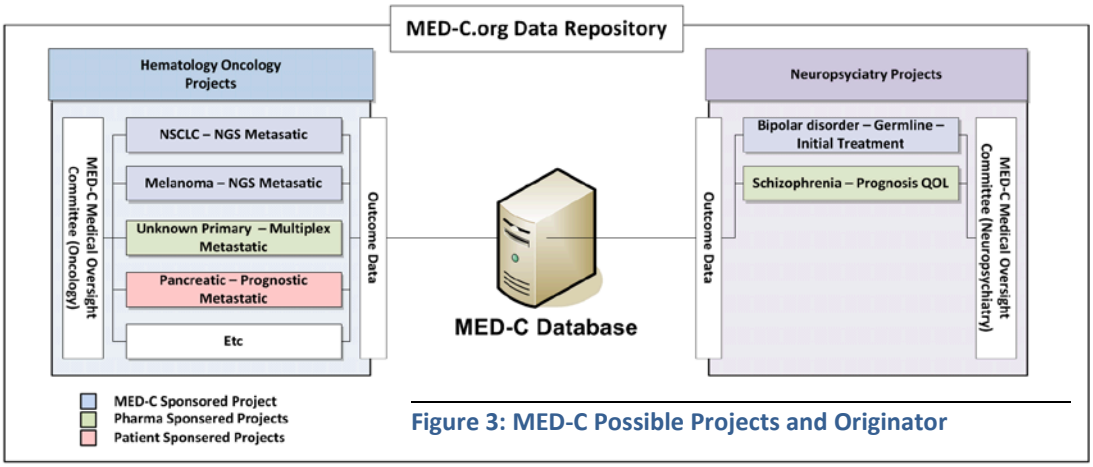

Figure 3: MED-C Possible Projects and Originator

molecular and clinical outcomes along with quality of life and patient reported data.

MED-C Project Development

Once MED-C leadership (in connection with advisory groups) has identified a potential project, the other groups are brought in.

MED-C Project Subcommittee(s) (MPS): Specialty specific committees will be formed as needed to discuss proposed projects and explore new efforts. Members include payors, patient advocates, physicians groups, industry representatives and regulators.

Initial Project Development: Once a project has been further explored, the existing (or in the case of a new clinical arena a newly formed) Medical Oversight Committee will review the proposed project and help identify and refine crucial elements. These could include inclusion criteria, testing methodology, treatment standards and endpoints.

MED-C Pilot Project: NSCLC - Metastatic - Next Generation Sequencing (N1N Protocol) (Figure 4)

Background: The National Comprehensive Cancer Network has recommended consideration of testing of tumor specimens in patients with metastatic NSCLC by next generation sequencing (NGS) beyond testing for EGFR or ALK. If positive for a non-EGFR or ALK mutation they recommend possible treatment with off-label targeted therapy. This recommendation was initially based on limited clinical data, mainly case reports or small series. In addition, the guideline stated that molecular medicine is integral to the advancement of treatment of lung cancer. The clinical basis of this recommendation does not meet evidentiary standard of many payors. Yet, many national thought leaders, patients and physicians want access to the testing and consider the testing as standard of care. Providers, especially in rural settings often struggle to obtain the testing and if mutation positive placing the patient on a targeted agent. Outside of a clinical trial drug is only available at high cost to the patient (or payor) or through compassionate use of the drug. In this process, no data (such as response or toxicity) is collected. In addition, patients may have to undergo new biopsy due to not having existing tumor tissue (which was depleted with initial testing). This adds the potential for morbidity and added cost to the payor.

N1N Protocol (or Registry): A patient with presumed metastatic NSCLC undergoes biopsy and a simplified surgical pathology work up is performed. If NSCLC is confirmed the patient is given the opportunity to enter into the MED-C N1N Protocol. If they decline then they are treated according to standard of care. If they agree, they are educated and a data sharing agreement is signed. They enter the registry and their tumor specimen is tested according to a cross-validated standard at an affiliated laboratory. In this case, the testing is would be done by instrument agnostic but validated multiplex panel such as NGS. If the tumor is found to fit a predefined mutation profile (such as a MET gene), the ordering physician receives a centrally defined group of molecular pathways specific to this profile, which also includes any clinical trials available (such as the Lung-MAP, or NCI Match trial). If they

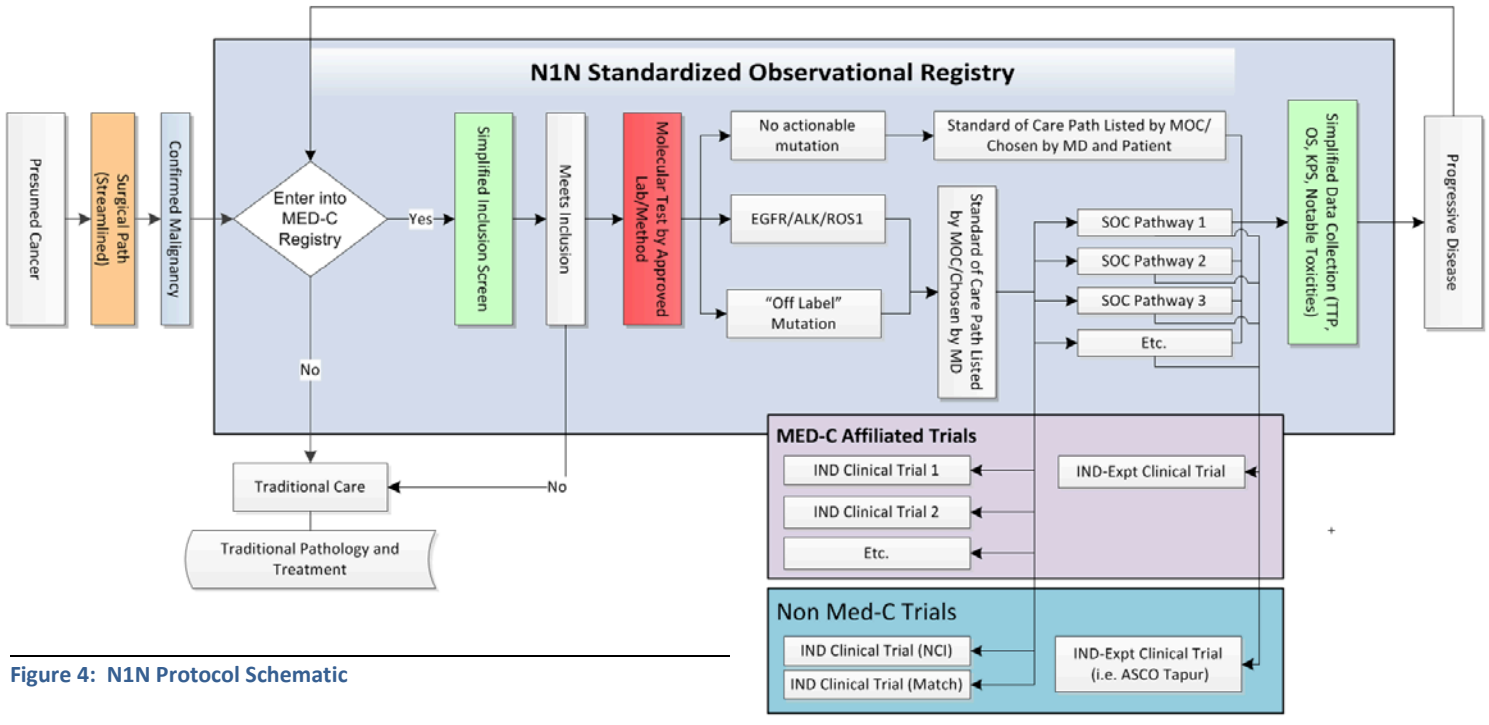

Figure 4: N1N Protocol Schematic

decline a clinical trial, the physician and patient discuss the options and treat according to one of the standard of care pathways provided. As long as equipoise is maintained, any off-compendia FDA-approved drugs could be provided as part of an IND-except trial or compassionate use program. The physician reports de-identified outcome data to the registry (type of treatment, time to progression, overall survival, and any grade 3 or 4 toxicities). The reported data is collected in a central database that is combined with data from the laboratory that performed the testing. Although not initially, the MED-C registry will add patient (or patient advocate) entered quality of life, outcome and additional toxicity information

Every few months, the Medical Oversight Committee will review outcomes from both inside and outside the registry to update treatment pathways. This iterative learning model will allow streamlining and modifying pathways to find the best treatments.

Benefits of the Project by Group

Patients: Patients want access to promising diagnostics and treatments especially in rural areas where they may not have access to clinical trials. The MED-C helps provide this access.

Physicians: Providers struggle with trying to get testing and drugs covered. In addition, most are not trained in anything but the most rudimentary aspects of molecular medicine. By having simplified ordering of testing, accessing advanced protocols and facilitated drug access for patients, care is streamlined. The time saved is much greater than the time to consent the patient and report the simplified outcomes.

Payors: Payors will save overall diagnostic cost by having streamlined upfront testing. Payors will have the ability to introduce new technologies in a controlled, evidence based fashion to their members.

As data is collected and mutations are understood, there is a systematic improvement of cost effective care by better understanding of who benefits from a given treatment and how to avoid unnecessary toxicity.

Laboratories: By allowing coverage with evidence development for promising technology, labs are able to introduce new and promising technology to patients. Also, the ability to integrate data from multiple labs as part of a larger project will demonstrate clinical benefit (and resulting coverage) quicker.

Pharma: As more targeted agents are introduced and with less frequent mutations, the number of patients needed to be screened in order to enroll in trials will become more difficult. By having a shared data collection initiative overall cost of research is decreased. In addition, the ability to have real world data will augment existing or future evidence portfolios, which will be useful to present to regulators and payors.

Regulatory Bodies: The rapid expansion of molecular diagnostics and associated targeted treatments has created a challenge for regulators. Some of these issues include: retrospective analysis of archived tissue specimens, smaller trial sizes, changing trail design (with higher levels of patient crossover), increasing costs of diagnostics and treatments, greater (and appropriate) emphasis on patient reported outcomes, etc. These issues have created a widespread call for "real world" data sets available to help define quality and utility of a given intervention. By developing a prospective interventional registry, with the ability to define the inclusion, treatment and the desired outcome elements, it provides ability to augment other data sets to round out many of the questions that regulators would like to see answered.

Unique Features and Overall Benefit of MED-C SOR

1) Shared governance and open data
2) Independence from a single institution, organization or group and a streamlined non-profit organization
3) Expandable and modular to all areas of medicine
4) High quality outcome data due to standardization and incentives to participate
5) Enhanced patient participation in research through encouraging enrollment in clinical trials or interventional pathways
6) Built in controls in pathways

Questions?

Q. Will the MED-C Registry cannibalize existing clinical trials?

A. In every treatment pathway if a clinical trial is available, it will be given as a treatment option to the physician and patient as a high priority. Trials such as those originating through the NCI, cooperative groups, professional societies, or disease specific organizations and others dedicated to high quality research will be affiliated with MED-C protocols. In many locations, especially in rural centers these clinical trials are not available. As of such MED-C.org will try to facilitate expansion of clinical trial sites, but in cases where this is not feasible, patients can be enrolled in the registry. The goal is to dramatically increase the number of patients participating in the advancement of care through trials first and standardized registry second.

Q. There are groups that are doing similar work, would it be better to expand one of these projects rather than build something new?

A. Where ever possible, existing infrastructure will be leveraged. But given the open nature of, shared governance and cross specialty focus of MED-C it likely to impact a broader community than any single group.

Q. Why run a registry, rather than a trial like Lung-Map or NCI trials?

A. Clinical trials, because of their specific data collection and focus, will always be the highest clinical priority of MED-C. Although trials are crucial to the advancement of care they are not available in many areas or patients do not desire to participate and are quite expensive. MED-C with it simplified inclusion screen, centralized methods of obtaining both testing and possible treatment, fits well with the practice infrastructure that already exists and gives another option for patients.

Q. Isn't this project an oncology, next generation sequencing endeavor?

A. Although likely starting with oncology and next generation sequencing, the infrastructure is such that it can be adapted to new technology and to other disease states. The testing, treatment pathways, and measured outcomes may change, but the MED-C infrastructure can be adapted and the methodology applied to many scenarios with different technology or different areas of medicine.

Q. What happens if a payor doesn't want to participate in a given clinical area, can it still go forward?

A. MED-C.org will strive to develop projects that are considered reasonable to a broad group of stakeholders. In rare cases where a potential project addresses only one stakeholder's needs (i.e. detailed toxicity evaluation for certain patients treated on a specific pathway requested by pharma), as long as these cases do not detract from the direction of MED-C.org and its other stakeholders these projects will be considered. A specific group will not be required to participate in a given project unless it fits well within their existing direction.

Q. Will the MED-C project only be limited to the U.S. and its territories?

A. Although the pilot project and initial structure will be run in the U.S. there is hope to expand or integrate this into international sites. Personalized medicine is an international endeavor, and many of the same clinical questions exist across borders. The larger the unified data set the greater the value.

Q. Payors have regulatory and even statutory rules around covering experimental treatment, so how can they participate in this endeavor?

A. Many payors will only cover that which is defined as meeting clinical utility. Standard of care in many areas of medicine (especially molecular) is constantly changing. Most stakeholders understand that the line between traditional and experimental care is blurring. In modern medicine, data collection is integral to patient care especially as it is used to demonstrate quality and effectiveness of treatments. Also, newer technology (such as NGS) often comes with more effective cost benefit than the combination predecessors it could replace. Reporting of additional genetic information is often at the same fixed cost for well-studied single mutations. Rather than not leveraging this information and given the potential value it adds to both current and future care, the MED-C registry leverages the routine and most promising advancing testing and associated care but also encourages advancement of molecular medicine research by organizing and leading participation in structured data collecting endeavors.