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Norman E. Sharpless, M.D.
Director
National Cancer Institute
9609 Medical Center Drive
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Re: NCI Request for Information, Strategies for Matching Patients to Clinical Trials (NOT-CA-18-063)

Dear Dr. Sharpless:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on the request for information regarding strategies to improve clinical trial matching. ACS CAN, the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, strongly believes that clinical trials are the key step towards advancing potential new cancer treatments from the research setting to the cancer care clinic, and that patient enrollment is critical to this success. Clinical trial matching improves enrollment by identifying a list of potential trials for which patients may be eligible. ACS CAN strongly supports NCI's ongoing efforts to improve both its clinical trials reporting program (CTRP) database and functionalities within trials.cancer.gov.

Clinical trial matching is the process of identifying a list of potential trials for which patients may be eligible. This is accomplished by collecting patient data and comparing it against the eligibility criteria of open trials in a database, resulting in a list of potential trials. NCI plays a dual role in clinical trial matching. First, through the CTRP database, NCI serves as a publicly available database of open cancer clinical trials, which is utilized by organizations offering clinical trial matching services. Through the trials.cancer.gov interface, NCI is also a clinical trial matching service, serving patients and providers by enabling them to identify potential trials.

In the U.S., there are two publicly available government databases used by matching services for cancer clinical trials – the National Library of Medicine's clinicaltrials.gov and NCI's CTRP database. Many matching services (e.g., Antidote, BreastCancerTrials.org, EmergingMed, Pancreatic Cancer Action Network's Clinical Trial Finder, Smart Patients) have found that information contained in these databases can be outdated, incomplete, or irrelevant to patients as they select a trial. These services further curate data found in either clinicaltrials.gov or CTRP using manual or automated (NLP, or AI)

techniques to create their own more structured database built off public data. This curation is resource intensive and the resulting data typically reside within the individual service or organization rather than being returned to the public domain. By creating more structured, accurate and complete data in the public sphere, NCI could significantly reduce the amount of redundant curation efforts going on today in the cancer community.

In addition to serving as a database of open cancer trials, NCI also offers matching services through its trials.cancer.gov interface. This interface serves two distinct audiences - patients and providers. The needs and goals of each audience are different. As a result, we encourage NCI to consider the needs of these different users as they continue to improve their clinical trial searching capabilities.

Patient-facing matching services target a subset of patients who are highly motivated and interested in learning more about clinical trials. While these matching services are important, studies show that only a small percentage (between 2.5 to 6 percent) of patients enrolled in clinical trials found their trials through such services.[1,2] This may be partly due to the smaller fraction of patients who are sufficiently aware of trials as an opportunity and motivated to conduct their own research as well as reflective of the goals of many matching services. Most matching services working with patients are not designed to actually guide patients all the way to enrollment, but rather their goal is to provide a list of potential clinical trials open for their cancer to be used as a discussion tool with the patients' providers. To avoid being overly cumbersome for patients, these services often use non-scientific language, and provide matches based on limited clinical data.

Matching services for providers, on the other hand, typically seek to identify clinical trials that patients are very likely to be eligible for based on a thorough assessment of a patient's clinical data. These services may have a significant impact on patient enrollment - research suggests that the majority of cancer patients who have participated in clinical trials (66 percent) learned of their trial either through one of their providers, or one of the study staff.[2] However, providers, especially those who are not at research institutions, are often unaware of clinical trials and have limited resources to help their patients identify the right clinical trial. Studies have shown that anywhere between 30 to 76 percent of eligible patients are not being asked by providers about participating in a trial.[3–7] Matching services can help improve provider engagement of patients around clinical trials by reducing provider burden in identifying potential trials for their patients. To be effective, however, they must employ detailed clinical data to ensure full eligibility determination and they must also be integrated into a provider's workflow.

In response to the Request for Information, we offer the following comments:

1. Structuring clinical trials information

Information in clinical trials eligibility criteria that can, and should, be structured, recommendations for structure, and importance.

NCI should prioritize standardization of eligibility criteria in the CTRP database based on:

- **The frequency with which a specific criterion is used in clinical trials.** By standardizing the most commonly used eligibility criteria (versus niche or less commonly used eligibility criteria), NCI can significantly decrease the amount of manual work that a patient and his/her healthcare providers must do to identify eligible trials. To make this more meaningful, NCI could consider identifying the most frequently used eligibility criterion by type of cancer. Other clinical trial matching services have found a specific cancer-type approach helpful when identifying the most relevant eligibility criteria.
- **Whether a specific criterion related to a potential participant may change during the course of a patient's disease trajectory.** Some clinical variables are mutable while others not. For example, white blood counts and glucose levels vary over time and ineligibility based solely on such a variable may be overcome with time and appropriate medical management. Similarly, an inclusion criterion that requires certain prior therapy could make a patient ineligible early during their treatment, but that same patient could later be eligible for the same trial after they had progressed through the required prior therapy. In contrast, an exclusion criterion based on prior therapy is not mutable and would make a patient permanently ineligible. Characterizing eligibility criteria by whether they render a patient permanently or temporarily ineligible could broaden possibilities for patient with otherwise limited trial options.
- **Biomarkers are increasingly critical to clinical trials, so structuring and making any biomarker requirements available is of high importance.**

As NCI structures data in the CTRP database, it is also important to note that the language of the structured data is critical to patient understanding. Data structured using medical ontologies will be inaccessible to patients.

Approaches for implementation and maintenance of structuring clinical trials eligibility criteria, e.g., Natural Language Processing (NLP), Artificial Intelligence (AI), human curation, etc.

Matching services currently use each of the approaches mentioned above (NLP, AI, human curation), but do so in different modalities. Some services do not attempt to change the underlying structure of the trials database, but use AI or NLP tools to probe unstructured data with every search. Other approaches involve making a copy of largely unstructured trial databases (clinicaltrials.gov or CTRP) and using NLP plus human curation to create a stand-alone structured copy of the original database. This allows more

basic search engines to explore the database. While proprietary search services have created databases with increased structure, these databases are typically only available through the service that creates them, which are often for specific cancer types. NCI could perform an important service by creating a more structured database across all cancers, and making this database accessible to anyone through a web-based search tool or to other developers through an API. To avoid duplicating work and to expedite the creation of a more structured database, NCI should work with services that currently perform such structuring (e.g., Antidote, BreastCancerTrials.org, EmergingMed, Pancreatic Cancer Action Network's Clinical Trial Finder, Smart Patients) to learn from their experiences and to explore the opportunity to incorporate into NCI's database the structuring work they already perform.

2. Facilitation of cancer clinical trials searching/matching

<u>Data elements in clinical trial eligibility criteria that are most meaningful for clinical trials searching</u>

Existing clinical trial matching services serve patients, providers, or both. While matching services for providers aim to identify an appropriate trial for a patient to enroll in based on a thorough assessment of a patient's clinical data, matching services for patients often seek to simply provide patients with a list of potential trials for their cancer based on simple searches to use as a discussion tool with their health care providers. As a result, patients are often presented with a long list of trials, many of which the patient is ineligible to participate in because the search was conducted with minimal clinical data. Increasing the clinical data points entered improves the match fidelity, but also increases patient burden. Many services have attempted to balance the ease of minimal data entry with the thoroughness of matching by requiring minimal data to conduct the initial search and then providing additional filters/data fields once the initial trial list is returned, thereby allowing those patients who are so inclined to further narrow their search.

The most meaningful eligibility criteria for trial searching are those that automatically disqualify the patient from participating in trials to help narrow the list (e.g., presence of a comorbidity such as congestive heart failure, biomarker status) versus ones that are potentially changeable (e.g., glucose level). The specific exclusion criteria often differ based on the type of cancer. Other clinical trial matching services (e.g., Antidote) have undergone extensive efforts to identify the most relevant exclusion criteria for specific cancers with the goal of presenting patients with a meaningful list of trials for which they are likely to eligible. Such an effort for all cancers would be beneficial.

In addition to eligibility criteria, it would also be beneficial to structure geographic data so that patients are able to filter clinical trials based on distance. Many services offer this functionality as part of the search process and enable users to filter clinical trials by selecting a limiting radius from specified point (e.g., within 25 miles of zip code). Patients often have extended networks of friends and family located in different cities where they might consider enrolling in trials, so geographic searching using multiple different anchor points would also be useful.

Presentation of patient information and the types of information as well as source e.g. human input into a website, Electronic Health Record (EHR) that will narrow clinical trial search/match retrievals to those for which a patient is most likely eligible

The incorporation of patient clinical data from the EHR is key to identifying appropriate trials. As comprehensive repositories of patients' clinical data, EHRs can closely match patients to trials that they are likely to be eligible for with a high degree of accuracy. To date, most matching services capable of integrating data from EHRs are designed to be used by providers rather than patients. While direct access to a patient's EHR would ease the search experience for patients by eliminating the need to manually enter complex clinical data, this type of integration may be difficult to achieve in a patient-facing service. This level of integration is also not necessary if the matching service is only intended for casual browsing of representative trials rather than seeking exact trial matches. However, EHR integration is a critical feature for matching services for providers, or for patient-facing services intended to lead to detailed matches.

Approaches for NCI to facilitate cancer clinical trials search/match (e.g. a simple interface on cancer.gov, contact center, etc.)

NCI currently serves as both a matching service through trials.cancer.gov as well as a robust database for other matching services to connect to and build on. This "front end" and "back end" differentiation is important to understand, as the design considerations for each of these roles is quite different. Structure, standardization and interoperability are key for the back-end database role, but the front-end interface on trials.cancer.gov must incorporate additional features to serve patients and providers. Areas where NCI could improve front-end functionalities on trials.cancer.gov include:

- **The use of patient-friendly language**. Standardization of conditions in the CTRP database may lead to the use of technical medical terms, but complex medical jargon is unlikely to be well understood by patients. The patient interface on trials.cancer.gov, therefore, must be designed to elicit the most useful information from the patient with the least effort, using patient-friendly language that can then be translated into more technical searches against the underlying data.
- **Giving patients the ability to create profiles and user accounts**. Many clinical trial matching services allow patients to do this so that patients can enter their information once and save the information in their profile for future searches. Such services can often collect more information from patients because they are able to save their profiles and come back with additional information (e.g., results from lab tests or imaging). Additionally, many services that allow patients to create accounts also often alert patients as trials that they may be eligible for become available.
- **More functionalities for providers**. There are numerous patient-facing search tools, including NCI's trials.cancer.gov, already available, but an area of strong need is for free or low-cost matching tools that can be utilized within the normal workflow by providers who are not

typically focused on clinical research. Commercial matching solutions exist, but small practices that do little or no research within their practice are unlikely to pay for services that result in referral of patients out of the practice. Interested providers can use free patient-facing services, but providers do not need the same level of terminology translation, and are typically looking for more definitive matches based on more extensive clinical data rather that crude matches based on a few questions that are more characteristic of patient-facing services. Providers also have the advantage of ready access to more detailed clinical data, but any matching tool must integrate into the provider's workflow and not require significant manual entry or extra work.

Approaches to automate matching participants to clinical trials (e.g. extensible clinical trials machine learning algorithms)

Providers are critical to improving patient enrollment – research suggests that the majority of cancer patients who have participated in clinical trials (66 percent) learned of their trial either through one of their personal providers, or one of the study staff.[2] Due to limitations in resources, providers often do not have the time to explore clinical trial options with their patients. As a result, as many as 76 percent of cancer patients who are eligible for a clinical trial are not being asked to participate, representing significant missed opportunities.[7] Automating the clinical trial matching process and integrating this into the provider workflow can help reduce provider work load. There are two main ways to automate this process, which include a passive approach and a proactive approach.

Under the passive model, matching is being performed in the background, and providers are alerted if their patients are potentially eligible for a trial. With this approach, clinical data from the EHR is being consistently run against open clinical trials to identify potential matches.

Under the proactive approach, providers must actively go to a matching service (usually through a link in their EHR). Data from the EHR can be run against open clinical trials once the matching service has been accessed.

3. Technologies and standards that may facilitate capture and transmission of information in structured format

Adoption of a shared language (or ontology) of systems interoperability to ensure research and development efforts are sustainable and scalable

Providers play a significant role in patient enrollment in clinical trials, but often have limited resources to engage patients about clinical trials. Therefore, it is critical that matching services for providers are integrated into the workflow and highly automated, requiring minimal time and effort. Interoperability between EHR systems and the CTRP database is essential to workflow integration and automation. This requires a shared ontology between clinical data systems and clinical trials data systems.

As NCI continues to identify methods of structuring data, it is important to note the distinction between shared language for interoperability and shared language that is patient-friendly. There are currently many standards and medical ontologies that can enhance interoperability (e.g., ICD-10, SNOMED), but they are different from ontologies that are useful for patient-facing tools.

4. Methods for fostering agile interdisciplinary collaboration, and, when applicable, public-private partnerships to advance modern culture of cutting edge research and development

There are several private entities today that have developed some robust matching capabilities. NCI should undertake an inventory and build on this work to avoid duplication of efforts. Innovations from the private sector include:

- Identifying and structuring the most relevant eligibility criteria;
- Presenting information about a clinical trial in a patient-friendly way;
- Providing additional information that is important to patients (e.g., treatment modality, anticipated number of visits); and
- Incorporating patient perspectives and experiences in specific clinical trials.

5. Approaches to facilitating and/or incentivizing structuring eligibility criteria in clinical trials protocols, as well as submission of structured information to the NCI Clinical Trials Reporting Program (CTRP)

NCI can consider updating the reporting requirements for registrants that must report in CTRP going forward while using tools like NLP, AI or human curation to structure previously submitted data.

6. Additional information, or factors, that should be considered on how can NCI best support and accelerate the ways in which patients find the appropriate cancer clinical trials and the ways cancer clinical trials may find patients?

There are two areas were NCI can provide significant value in clinical trial matching – as a database of open cancer clinical trials for other matching services and as a tool for providers.

NCI's CTRP serves as a robust database for other matching services. As a centralized repository with one of the most comprehensive listings of cancer clinical trials, NCI's database is an invaluable data source that can be used by a wide array of third parties. However, to date, many matching services do not look to NCI as the source for their cancer clinical trials database. NCI could consider growing in this area by:

- Providing more visibility about its database of clinical trials. This include clarifying if/how the cancer clinical trials listed in the NCI database differs from the cancer clinical trial listed in clinicaltrials.gov;
- Incorporating non-NCI funded trials into the database;

- Continuing with the structuring of eligibility criteria; and
- Providing additional data about the trials, including data that cancer patients may care about (e.g., treatment modality, anticipated overnight stays)

In addition to serving as a database, NCI's interface on trials.cancer.gov could be better leveraged to serve providers, who have an outsized impact on patient enrollment in trials. There is currently a dearth of publicly-available tools tailored to the needs of providers. We believe trials.cancer.gov could help fill this need and encourage NCI to continue to build out functionalities for providers.

Conclusion

On behalf of the American Cancer Society Cancer Action Network, we thank you for the opportunity to comment on the request for information. In addition to our comments, we are also appending an ACS CAN whitepaper, An Analysis of Cancer Clinical Trial Matching Services, that summarizes matching services as an additional reference. If you have questions, please feel free to contact Shelly Yu (shelly.yu@cancer.org) or Mark Fleury (mark.fleury@cancer.gov).

Sincerely,

Lisa Lacasse
Senior Vice President
ACS CAN Strategy & Operations

Attachment: "An Analysis of Cancer Clinical Trial Matching Services"

Citations

1. Gansler, T. et al. Outcomes of a Cancer Clinical Trial Matching Service. J. Cancer Educ. 27, 11–20 (2012).
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