Clinical Trials - Science BRP Working Group Report

What is the recommendation (1-3 sentences)?

Many thousands of cancer patients have been treated with similar standard of care regimens. Some have had outstanding responses with substantial prolongation of life or cure. Some had early outstanding responses but with relapse and resistance to continued therapy with the same agents and ultimate death. Some have had minimal or no response with no prolongation of life. Many thousands of formalin-fixed, paraffin-embedded tumor samples from patients that have received standard of care—that is, care provided in the clinical trial setting—are available for molecular analysis to determine what parameters correlate with an outstanding versus dismal response. By *fully analyzing samples already available* from thousands of patients receiving standard of care, it will be readily possible to develop hypothesis as to which patients will benefit and which patients will not benefit and thus which patients will need to receive experimental therapies early on.

Analysis of tumors from thousands of patients already treated with known outcomes, will allow for rapid development of hypotheses to be *validated prospectively in clinical trials*. Identification of categories of patients destined to not benefit from standard of care will also lead to a better explanation as to why adaptive resistance occurs and should accelerate studies to find regimens to circumvent adaptive resistance. The result will be less treatment for some patients, reclassification of others into a new set of risk criteria, and the ability to focus therapies and therapeutic research on the patients with the highest risk cancers.

Where are we are now?
Summary of the current state of the science/practice

Assumptions:

- By generating and analyzing extensive molecular and microenvironment assessment of tumors from patients already treated by standard of care, parameters that correlate with success or failure can be derived within several years. Prospective collection of samples is imperative, but assessment of tumors already in hand from patients already treated will provide substantial information in a much shorter time.
- Opportunity will likely define what patients are likely to benefit from standard therapy, what patients are unlikely to benefit and require additional or novel interventions.
- Complementary to the other areas of focus in this Planning Committee – response prediction, genomics – research can be designed to change the standard of care.
- We propose five (could be 6) clinical disease stratifications in which research questions could be explored, and suggest that tumors from 1,000 patients in each category be fully analyzed and patient records be used to annotate the outcomes:
  - o Cancers surgically resected with high (80% or more) likelihood of cure
  - o Resected cancers with high risk of relapse, generally treated with adjuvant therapy if applicable (maybe = MRD in leukemias)
  - o Cancers that are localized but unable to be resected
  - o Previously untreated metastatic disease

o   Metastatic disease with acquired (or primary) resistance.

Each of these subsets span cancer types, and for each a subset of scientific questions might be addressed, with examples as follows:

Stage	Opportunity	Sample Trials
Resected, high likelihood of cure	Define characteristics of favorable outcome.	Poor-risk genomic phenotype in ostensibly good-risk category: test: more intensive treatment
Resected, needs additional therapy	Analyze characteristics of cancers of relapsers versus cures. Define genomic classification complementary to current (usually morphologic) risk definition. Better definition of high risk patients, and identification of targets for treatment.	1. Good-risk genomic phenotype after surgery for a higher risk tumor: trial of adjuvant versus no additional therapy 2. Poor-risk genomic phenotype even with adjuvant therapy: use findings to suggest different therapy, immunotherapy. 3. Studies in breast cancer (Tailorx 10,300 patients, MINDACT 6700, Clalit 2000) show feasibility
Locally-advanced unresectable	Identify characteristics of those who respond (generally higher response rates than with metastatic disease), and those who don't. The nonresponders can be considered for novel treatment proposals in which some of these patients can be cured.	1. Data mining of poorly responsive locally advanced malignancies in which new approaches can be employed 2. Clinical trials directed at subsets of patients based on DNA or RNA mechanisms of action 3. Opportunity here especially for immunological approaches, and perhaps resectability at a later stage would be adjuvant to the systemic therapy.
1st line metastatic	Define biological basis for variable response, and targets that evolve and prevent cure. Encourage proposals that would define sensitivity and resistance using bioinformatic analyses to adduce information.	1. Few impactful studies exist in this arena; evolving technology may now permit more insightful analyses. 2. Chemotherapy response rates are rarely > 50%. Identify non-responders as early as possible, and identify their biological characteristics to identify targets for novel investigative approaches.
Recurrent/resistant metastatic	Primary resistant tumors may be highly informative for biological informants of drug-independent resistant behavior. Relapsed tumors following initial therapy are likely to have a limited number of resistance strategies, most of which for standard therapies are poorly defined.	Secondary (adaptive) resistance tumors could be examined for genomic changes over time, correlates of adaptive resistance, and identification of mechanisms of resistance and mechanisms to overcome resistance..

- Identification of good- and poor-risk characteristics across disease stages will suggest testable models of tumor progression. Tumor biology will drive clinical trials in cancer therapeutics.
- Cross-cutting genetic and genomic themes will help to address tumor microenvironment, immunophenotypes, stem cell remnants, heterogeneity, and DNA damage response/signaling.

- Several groups (e.g., Children's Hospital of Philadelphia) are engaged in retrospective analysis of biorepository samples, and others (e.g., members of the NCI Clinical Trials Network [NCTN]) are interested but have limited resources. Partnerships could be formed to share outcomes data and other data.

What are the clinical trials? Specific examples:
Good Prognosis Adjuvant Setting:
- Genomic analysis of 1000 patients in four diseases. These tissues may be available with outcomes in existing banks. Define profiles of risk, high and low. Example in colon cancer: E5202 has about 1900 patients with Stage II disease. Risk of relapse in this stage is about 20%, and standard treatment is no therapy in the absence of adverse risk factors. Develop high vs low risk profile.
  - *Sample trial: Colon Cancer Stage II.* Patients selected by MSI status and p53. About 75% received chemo +/- avastin. Results not yet available. Proposal would be to subject the samples from the non-MSI patients to whole exome sequencing (at a minimum), and gene expression profiling. miRNA and limited proteomics also possible. Here we want to find markers of patients who do poorly (we would expect relapse in 15-20%), and identify that profile. The clinical trial would then apply that profile (having validated it internally in the study first, and later in another trial population), and use it to conduct trials of promising interventions looking for big effects.
- In low risk, a *single arm observational study of NO TREATMENT* would target a 5-year recurrence rate of less than, say, 2-4%. This trial would be part of the difficult goal of proving *utility* of the test. This would need to be a simple test conducted in the community, with various design issues to guarantee integrity of the intended approach.

The following table gives the 95% confidence intervals on the 5-year recurrence rate for different observed recurrence rates and sample sizes.

Observed Rate	n=500	n=1000	n=2000
2%	(1.0%, 3.6%)	(1.2%, 3.1%)	(1.4%, 2.7%)
3%	(1.7%, 4.9%)	(2.0%, 4.3%)	(2.3%, 3.8%)
4%	(2.5%, 6.1%)	(2.9%, 5.4%)	(3.2%, 5.0%)

For a test, if the null hypothesis is taken to be the smallest unacceptable recurrence rate, and we want to have good power (say 85%) to reject the null rate in favor of a smaller recurrence rate when the true rate is 2% smaller (ie 6% vs. 4%; 5% vs. 3%; or 4% vs. 2%), then the sample sizes needed for a one-sided 2.5% test are 1091 for 6% vs. 4%, 874 for 5% vs. 3%, and 676 for 4% vs. 2%. Actual sample sizes would be larger, depending on assumptions about drop out, etc.

Good-risk genomic phenotype after surgery for a higher risk tumor:
- Genomic analysis of 1000 patients in four diseases. Again, for some of these tissues are already available to begin analysis in year 1. Here we want to identify patients who do well.
- Again example in colon cancer, tissues are available.

Sample trials:

I. Genomically-Defined Good-risk Patients: Phase III trial of therapy versus no therapy – this is well-established as a feasible design (TAILORx in breast cancer for example). The goal would be equivalence, defined here as an advantage (in 5-year DFS) of less than 3-5% for treatment. TAILORx was powered to detect a decrease of 3% in 5-year DFS (from 90% to 87%). In this noninferiority setting, if the null hypothesis of no difference is used (that is, the null is equivalence), then it is conventional to use larger type I errors and higher power than in superiority tests. With 10% one-sided type I error and about 95% power (conventional for this design), to detect 90% vs. 85%, 232 events would be needed; for 90% vs. 86% 323 would be; and for 90% vs. 87% 515 would be. If one plans on 10% of the cases having events at the time of final analysis, this would give sample sizes about 10 times as large as the number of events.

II. Genomically-Defined Poor-Risk Patients: An unselected population that receives chemotherapy has a 30% chance of relapse in 5 years. The genomically-defined population would likely identify those with say a 60-70% risk. Here we would anticipate that small trials should yield strong effects, and that the treatments tested would themselves be guided by the genomic testing, and would include immunologic therapies. Trials here would target big effects (Hazard Ratios of 0.6 or less), and could be accomplished in studies of 300-600 patients per study.

Locally advanced, non-resectable tumors
- Genomic analysis of 500-1000 patients in specific diseases in which this stage of disease is relevant – examples include lung, esophageal, H/N, breast, pancreatic, sarcomas, cervical, rectal. Pick 4-6, and conduct an observational study in the real world. The endpoints here are in real time – tumor shrinkage, or rendered operable, yes/no. In the non-responsive group, the biology of that class would ideally drive the next set of interventions. For example, if the resistant patients have a mesenchymal profile, that group might be targeted with EMT-directed interventions. Since radiation is a part of many of the treatments of these diseases, insight into radiation resistance would emerge from these studies. These trials would be smaller studies with intensive tissue sampling and/or imaging, designed to elucidate biological processes underlying both response and resistance.
- 1st line metastatic – exploration of newer and more effective therapies in subpopulations
- The landscape for targeted drugs is well-covered, but not for the more standard chemotherapy drugs that are still an important part of therapy
- Potential to fund studies of tumors receiving standard therapies, potentially to complement, in many diseases, the adjuvant trials described above

- Resistant disease – exploration of mechanisms of resistance, trials directed to target common mechanisms of resistance with a goal to delay onset of resistance.
- Trials of standard therapies in several tumors – for example rituxan in lymphoma, using pre/post biopsies in sufficient numbers of patients – perhaps 250-500.
- Studies are most relevant for highly effective therapies, chemo/targeted/IO
- Goal should be to consider tumor/TME/immune responses

Identify barriers to progress and/or emerging opportunities

- New drug studies are well-resourced, and have the power of pharma funding to ensure completion. However, the bulk of drug-based cancer therapy is already established, but the basis of success, the definition of who should be treated, and the approaches that might make them better, remain relatively unstudied
- Only 5% of all patients enroll in a clinical trial. Barriers including clinic infrastructure, medical oncologist reimbursement, and patient reluctance to enroll in trials should be considered.
- While barriers exist, over 2000 institutions/consortia/practices participate in the NCTN and meet the enrollment criteria for continued membership. This mechanism should be pursued in ongoing clinical research efforts, including better development of quality metrics, reimbursement of time, and inclusion of contractual and regulatory structures that are well-established, functional and inexpensive.
- The strengths of the system are willingness of oncologists and patients (800 pats screened on MATCH trial in 3 months) to engage in clinical trials, use of standard treatments as appropriate, uniform management of cancer care, agreed standards, and available tissue for research and diagnostic use.
- Missing from this system are: (1) Appropriate bandwidth for oncologists to recruit patients, lack of nursing and research team resources to recruit patients, provide informed consent, and organize sample acquisition, which could be solved with research reimbursement for patient accrual. (2) Ability to consistently collect tumor specimens from treated patients, lack of sample preparation/block selection (need pathology support), challenges of shipping to central labs and conduct tumor assays (central support).
- The Cancer Genome Atlas (TCGA) database may not have the clinical data necessary to support the retrospective studies. For example, imaging data were never captured in TCGA. Careful consideration should be given to determining whether genotyping is feasible and logical as part of standard of-care in clinical trials, and whether the quality of the data generated will be acceptable for other applications, such as RNA-seq.
- Challenges related to sample quality and performance need to be overcome. A pilot study or demonstration project could test the quality of biorepository samples.
- The recommendation provides opportunities to: (1) discover new molecular targets of response using well-annotated samples from patients who were treated with traditional chemotherapy and radiation (results from the NCI's Exceptional Responders Initiative

would be useful); (2) better stratify patients into various treatment arms in trials; and (3) determine patient response to treatment in many contexts.

Where do we need to be (in 1-5 years)?
- In depth analysis of existing resources from clinical trials in various stages, with a 2-year delivery time
- Fast-track analysis of clinical trials based on these profiles to challenge current therapeutic strategies: 1 year development, 2-3 years accrual.

Rationale for investing (Why is this priority ripe for accelerating?)

Opportunity brought about by recent development in science, technology, practice
- Emergent and established technologies bring together clinical priorities
- Bringing SOA omic/other technology have the promise of redefining cancers in a targeted fashion, which parenthetically define the utility of these technologies themselves
- Clinical research projects can dovetail with other proposed priorities

Does it address an unmet need or important gap in knowledge or practice?
- One major need is to understand treatments currently administered. For example, with adjuvant therapy, 100% of patients with a particular disease stage receive treatment, yet only 10-20% benefit. Of the 80%, many are already cured and may not require treatment, while some are going to relapse regardless and should receive different treatment.

What would be needed for success?

- **New or expanded resources –** Leveraging the existing system to reimburse current work and further expansion of clinical trials.
- **Barriers/roadblocks eliminated or reduced –** The shortage of committed medical oncologists and lack of reimbursement are major barriers. An interdisciplinary team approach is essential with appropriate reimbursement mechanisms in place.
- **Workforce training –** Current structures exist, but further education is needed regarding genetic and genomic implications of cancer treatment and clinical trial development. Team communications, interactive patient education to facilitate consent, and engagement of diverse populations will expand clinical trials to this novel platform.
- **New or enhanced technologies –**omics is/are the key. The MATCH trial provides a model for trials with genetic and genomic assay analysis, with extensive validation across sites to assure reliability.
- **New scientific approaches –** the plan integrates new scientific approaches throughout.
- **Structural/behavioral/societal changes –** expansion from current methods is the springboard for change.

Strategy: What will it take to get there?
Issues to consider

- Nature of genomic characterization. What depth – Hotspots, WES, WGS, DNA methylation, Expression profiling, miRNA, proteomics? Does it need to be uniform across proposals? Cost?
- Envisage research platform conversion to commercial test (learn from Oncotype-DX)
- Number of patients needed for characterization to power initial tests of treatment strategies?
- Distribution of tumor types? How not to get overwhelmed with the four common cancers?
- Will RFP/RFA's ask for tumor type focus, or breadth across cancers?
- What is the order of magnitude of patients accrued for observational endpoints?
- What will be the timing, size and scope of the clinical trials?

Concrete actions to take in the next 1-5 years

- A one-year embarkation will ensue – negotiations, decisions about the new risk stratification categories and related clinical trials.
- Real world patient accrual, set up of central resources (study structures, data elements, database, registration procedures, sample acquisition procedures, nucleic acid and protein extraction, pre-analytics, assay validation, ongoing communications with patient and oncologists, among many), tumor testing, documentation of treatment, and early outcome data for some categories yrs 1-3 of funding.
- Trials in patients with advanced/resistant disease can begin year 1.
- Trials in locally-advanced disease depending on strength of evidence could also begin early, year 1 or 2.
- Trials in the adjuvant setting would rely in part on information obtained as part of the set of observational studies. Technology could be applied to the well-curated specimen banks that exist in the legacy cooperative groups of the NCTN. These would provide the fastest route to the initiation of trials addressed to adjuvant strategies in newly-defined sub-populations. Feasibility of this approach has already been established (as in the MINDACT breast cancer trial, which addressed risk categories on clinical versus genomic grounds).

What does success look like?

1. Better risk stratification of cancers– allows treatment to be tailored on those who at highest risk for relapse
2. Better definition of poor-risk versus good-risk at a biological level will indicate potentially useful therapeutic directions and allow smaller trials to evaluate them.
3. Greater success in curing locally-advanced cancers.
4. Better understanding of response in advanced cancer.

BRP "Clinical Trials" Working Group Proposal
A Network for Direct Patient Engagement

The recommendation (in 1-3 sentences)? Develop a simple mechanism to provide comprehensive tumor profiling (genomics, immune cells and microenvironment) for all high risk and advanced stage cancer patients for a period of 5 years; the profiling would be implemented in a federated model that could link many labs accepting certain standard operating characteristics and quality controls, as well as data glossaries to ensure data compatibility. Through profiling, patients could be contacted to allow matching to new "smart therapy" options, as through a pre-registration system to accelerate clearance into the right trials for the right patients at the right time.

This would be linked to a novel, simple and straightforward national consent to allow patients to "donate their data" on clinical outcomes so that profiling and clinical characteristics could be linked.

Enlist direct engagement by cancer patients through multiple existing and new channels, both on and off conventional "intervention clinical trials," to volunteer for this nationally federated and shared database to collect genomic data as well as conventional pathology and other descriptors, along with the ability to track and match clinical inflection points and outcomes. To avoid patient selection bias, develop educational tools and incentives to more fully engage community oncologists in clinical trials. Develop composite profiling of tumor with genomics as well as microenvironment descriptors (including tumor immunoprofiles and infiltrates).

For patients willing and able to provide serial biopsies at clinical inflection points (pre-Rx/on Rx/at progression), this "multidimensional molecular/cellular/tissue profile" could inform research on various classes of therapeutic agents. Use "recognition" technology to match patterns to specific cancers, similar to "big data" projects used in defense/anti-terrorism/astrophysics to develop a new ontogeny of clinically relevant cancer groupings by pathways and profiles. To further increase the value of patient profiling data and provide compelling efficacy data, identify actionable items early, such as pairing profiling data with new cancer drugs.

> ### Summary of the current state of the science/practice:
> Since genomic profiling of tumor has demonstrated importance for understanding tumor heterogeneity and identification of genetic alterations that may allow for precision medicine therapeutics, expansion of the diagnostic pathology report to include advanced molecular profiling of the cancers in all patients will be a transformational endeavor. Matched drug availabilities and combined modality protocols could be accessed by the treating oncologists. This system will allow for potential therapeutic interventions earlier in a patient's cancer journey, rather than late in the process. This is most definitely not a monolithic "top down" model that we propose, but rather a flexible, interactive and federated system of tumor profiling linked to clinical data repositories to link molecular data with associated clinical outcomes for patients.

Genomic profiling (limited panels, larger panels, Whole Exome Sequencing, Whole Genome Sequencing) is already technically feasible but limited to patients who can pay, or in clinical trials which rarely share data across centers and sponsors. This is all technically feasible with appropriate engineering at social, economic and organizational levels. Multiple platforms for tumor genomic profiling are available; however, no standardized approach is universally accepted. Also, there is no standard accepted quality assurance methodology nor accepted Information technology standards that allow for federated databases to talk with one another and cross-reference data. A standardized next-generation sequencing panel for profiling patients that includes validated tumor and germline gene panels as well as panels to investigate the immunogenome would be useful.

Identify barriers to progress and/or emerging opportunities:
Cost of obtaining tissues and obtaining quality tissue samples for genotyping needs to be addressed. Consent issues need to be addressed as simply and straightforwardly as possible, with a consent that is "one and done" for tumor analyses, future research and data collection and use. Patients can be engaged without necessarily requiring physicians to serve as the sole portal of entry to this large open-sourced study with appropriately mechanisms to support important operational details of tissue collection, processing and data transfer. There is no standardization of the platforms, tumor collection, processing, utility or data warehousing. However, NCI clinical trials network groups (ECOG/ACRIN in the NCI MATCH trial) have developed some processes for obtaining tumor tissue, shipping to analytic centers, and providing genomic results to the treating physicians with a turnaround time of approximately 2 weeks. This experience shows that this is a feasible operational, and the reception by patients and community oncologists has been very positive to date with rapid accrual. The committee is proposing a federated effort with defined operating principles to allow many labs and centers to perform such profiling and data collection, with quality and data-dictionary standards, so that the whole will be greater than the sum of any component parts. This will also overcome capacity bottlenecks which would be inherent if only one large site were to perform all tissue analyses for the country.

The opportunity exists to collaborate with other groups doing similar work to consolidate useful clinical information. Many repositories are not equipped to handle clinical data. The data systems could be linked to the NCI Genomics Data Commons or other new Cancer Moonshot initiatives such as the patient-focused volunteer CancerBridge database system. Other initiatives such as the GENIE project also work to enhance sharing of clinical data.

Challenges exist regarding the interpretation of clinical trial treatment and outcome data for patients, providers, and other stakeholders. Existing initiatives, such as the American Society of Clinical Oncology's CancerLinQ and Flatiron Health's platforms on oncology, could serve as models to improve interpretation.

Decision support is needed to provide real-world evidence. Having such evidence would provide the opportunity to develop innovative tools that could facilitate the gathering of

data (e.g., using patients' digital devices to provide a continuous flow of patient-reported outcome (PRO) data).

Where do we need to be in 1-5 years?

Key research priorities:
1. Nationally federated database built from standardized and interoperable components of cancer profiles and patient phenotypes (outcomes).
2. Matching to clinical trials at national scale, with definitions of go/no-go milestones to ensure success continues and marginal utility testing is stopped.
3. Public-private federated model for tumor profiling, matching to relevant trials and identifying with precision the full scope of anticancer activities across cancers at a national scale.

Rationale for investing: Why this is the best opportunity to invest at this time!

- **Opportunity brought about by recent development in science, technology, practice:** Although profiling is already feasible and in limited deployment, a shared national effort with aligned goals to maximize current opportunities will avoid slow pace and poorly organized, hit-or-miss individual center/individual sponsor research efforts. There is also the fairness argument in favor of doing this at national scale, since offering a national program of tumor profiling and data sharing will be more fair to disadvantaged patient groups and those with limited socioeconomic means.

- **Does it address an unmet need or important gap in knowledge or practice?** Absolutely yes. Pre-registration of profiles will create a "pre-check" mechanism for cancer therapies and cancer clinical trials for defined subsets of patients that will allow us to tell our patients more about expected risks/benefits. Pre-certifying patients on any level will improve our understanding of unselected trials, and will facilitate finding the rare but "low hanging fruit" in which single mutations could be targeted with life-improving impact for patients. This will also allow machine learning to identify patterns important for rational combinations and synthetic lethal opportunities with new agents and strategic orthogonal targeting. We would also be able to assess where such profiling adds no value, and stop such subsets from proceeding wastefully with ongoing analyses of the data over a 5 year period in relatively "real time."

What would be needed for success? *For example*:

- **New or expanded resources:** national scale with CMS coverage and infrastructure to move quickly to expand what is considered a "standard" diagnostic work-up. "*Move beyond the microscope and tell me more about MY cancer*" can be the battle cry for our volunteer army of patients who want to contribute to a national charting of the cancer landscape towards precision cancer diagnoses and the best possible options for care. The rapid accrual to the NCI MATCH clinical trial in the

community already attests to the untapped demand for this testing, and the opportunity to accelerate knowledge creation and help patients faster through a coordinated national federated effort. This proposal also aims to be a responsible steward of resources by focusing on developing analytics to assess in which clinical settings such profiling is having positive impact, as well as to stop profiling efforts if there is no demonstrable impact.

- **Barriers/roadblocks eliminated or reduced:** only the privileged can currently access molecular tumor profiling. This is inefficient, unfair, and scientifically unjustifiable. A national effort is efficient, fair, and maximizes the chances of successful outcomes and data collection with analytics in 5 years.

- **Workforce and public trained:** genomic education is necessary for the workforce as well as the public. Patients need to be educated that a modern definition of cancer includes these important aspects so that we can together define these diseases with more precision, and their own outcomes may change. They are also part of the team building this important "data railroad" for cancer across the country to improve the way we transmit information and learn about cancer. Training "on the cancer journey" is most effective, and this effort will accomplish this.

- **New or enhanced technologies:** new incentives to merge with data sharing and other groups, as well as new incentives to improve technology of tumor processing and profiling (as in the High Tech Sector) from this national initiative.

- **New scientific approaches:** epigenomic profiling will take off soon, and this can build upon the genomics foundation. Efforts to use genomics to assess immune infiltration and T cell repertoire are similarly in development and being done on a smaller scale. The wealth of information from a broadly annotated population is an opportunity we cannot miss.

- **Structural/behavioral/societal changes:** closer interactions will evolve between patient/advocacy groups as well as academics, community oncology practices, governmental researchers, regulators (with a focus on quality "real world evidence") and resources, as well as the biopharma/industrial sectors and IT sectors.

Strategy: What will it take to get there?

Concrete actions to take in the next 1-5 years: Develop processes to standardize technology, tumor handling, expand treatment protocols and implementation for accessibility, and create Health IT to manage data and simplify transfer.

Develop a mechanism to cover the costs (not charges) for profiling as a "standard cost of doing business" in cancer care. Insurers benefit from research – consider adding a line item for a research fund contribution as a mandated cost of providing insurance products in this country (this concept will be put into our committee's policy recommendation as

well). From a policy standpoint, it is also important to link this to a delay in implementing any new restrictions on the Common Rule for Research on Human Participants. There are important unintended negative consequences.

What does success look like? Success measures include a clinical report that includes individual patient tumor genomics and other cancer characteristics with a defined standardized data terminology and a shared database, federated amongst interoperable components, to allow analyses and linkages between patient and tumor characteristics and clinical outcomes (benefits and toxicities).

A national database, several new drug successes, and much information about what does and does not work in trials as well as in the "real world" of practice. Additionally, this resource will allow researchers to probe mechanistically WHY certain treatments are succeeding or failing in profiled patients. Patients will have a reservoir of data against which to compare their personal profile and understand their own disease, and their family profiles as well. Faster development of new agents with a robust biopharma sector contributing new agents at affordable prices (decreased cost to approvals) while maintaining healthy profit margins and attracting new investments in cancer research and development. Rare subsets can be grouped effectively into robust markets to encourage drug development for pediatrics and parsed subsets of common diseases (even rationally-defined mechanistic subsets of triple negative breast cancer, brain tumors, or gastrointestinal cancers, for example).

Impact on patients: Done at the national scale and scope, this would be profound and potentially game-changing for cancer care and research, as above. Better engagement, better understanding, better outcomes.

Why is this not "Business As Usual"? This is much different than the current unfair, fragmented, inefficient system in place that limits access to technology and only gleans a small subset of data from the massive heterogeneity of cancer patients in the USA. And – with coordination and a series of public/private partnerships, this is perhaps not all that much more costly to execute than the current fragmented and limited systems duplicated across many cancer centers in the US at this time!

Demonstration Project to Develop New Technologies

What is the recommendation (1-3 sentences)?

Implement innovative scientific approaches, particularly through the development of new technologies, that rapidly prioritize the selection of effective therapies for individual patients, based upon the empiric response of that patient's tumor to therapeutics. Recent exemplars include intra-tumoral microdosing devices that are briefly implanted in a patient's tumor prior to surgical resection, and patient-derived organoids to simultaneously screen many drugs in vitro.

Where are we are now (2-3 paragraphs)?

- Summary of the current state of the science/practice

    - Prioritization of drug candidates during preclinical and early clinical development is typically based on activity profiles across cell lines, xenograft and PDX models, often focused on a specific genomic context (e.g. driver mutation) that forms the basis for the drug target. Although there have been many successes with this approach (most approved targeted therapies), it is limited by the availability of models that are "validated," i.e. predictive of clinical benefit in patients represented by that set of models. Large swaths of human cancer are not currently modeled by existing cell lines and xenografts, despite significant efforts to expand the number of cancer cell lines (e.g. cancer cell line encyclopedia, etc).

    - In vivo multipore drug dispensers have been fabricated and evaluated in preclinical models. The devices are capable of dispensing small amounts of drugs separately and in combination, such that a small number of cancer cells near the pore are exposed to drugs. Surgical removal of the device after several days, and co-registration with the nearby drug depot, identifies active therapies that promote cell death.

    - Patient-derived tissue models can be rapidly derived from normal tissues and carcinomas such that molecular and simultaneous multiplex therapeutic profiling can ensue. For example, early results from colon cancer organoids and conditionally reprogrammed cells in feeder culture suggest that therapeutic response of patient-derived tissue models to standard cytotoxic agents is predictive of the patient's clinical response.

- Identify barriers to progress and/or emerging opportunities

    - The microdosing implantable devices are only beginning clinical feasibility assessment, and such devices could also be used to evaluate biologics including immune modifiers. Since surgery is not always possible in sick cancer patients, the fabrication of such devices and alternative approaches to capture the same

information when surgery is not possible represent technology development opportunities (e.g. microscale CTC capture, cell-free nucleic acid, nanosensors).

- Patient-derived cultures have not been established from all human cancers to date. For example, organoids have not been established from all human cancers to date (e.g.: GBM, primary prostate), and they currently do not include elements of the tumor stroma that may impact therapeutic efficacy. Current 2D co-culture and 3D organoid protocols can take weeks to months to generate enough samples to do deep molecular and therapeutic assessment, representing opportunities for technology development. Patient-derived cultures represent model systems to evaluate personalized immune-oncology approaches, such as the identification of neoepitopes and Adoptive Cell therapies. Finally, as normal tissues such as liver, heart and intestine are being grown in microscale formats for predictive toxicology, both efficacy and toxicity platforms could be used synergistically to personalize a therapeutic index.

- Expanding the recommendation to include a Phase 0/Phase 1 platform would further advance pharmacology efforts. A novel technology that would indicate the benefit of a clinically administered dose would be transformational; a device that could obtain profiles (e.g., cytokine profile) at metastatic sites in a tumor would greatly accelerate the drug qualification process. Insight into effective combination therapies for patients would be critical for developing new predictive models and could serve as an interface between technology and drug development.

Where do we need to be (in 1-5 years)?

- Key research priorities (pick 2-3)

    - Clinical trials to evaluate the safety and predictive ability of intratumoral microdosing/monitoring devices to pick effective therapies for patients.

    - Clinical trials to demonstrate the feasibility of organoids to choose drugs prospectively for cancer patients.

    - Clinical trials to evaluate the ability of implantable devices and organoids to address therapeutic resistance/dormancy in patients.

    - Preclinical studies to explore broader application of patient-derived cultures including technology, shifting the focus to short-term drug sensitivity readouts using high-throughput and high-content imaging, flow cytometry, CyTOF (versus waiting for establishment of a serially passaged organoid lines) and the inclusion of stroma and immune infiltrates (versus pure epithelial cell cultures) to evaluate drugs targeting the microenvironment.

- Rationale for investing (Why is this priority ripe for accelerating?)

- Opportunity brought about by recent development in science, technology, practice

  - Emergent technologies

  - Microdosing implantable devices recently developed.

  - Organoids are a very recent breakthrough to robustly culture human normal tissues and neoplasms.

  - Does it address an unmet need or important gap in knowledge or practice?

    - Yes.

- What would be needed for success? *For example*:
  - New or expanded resources
  - Barriers/roadblocks eliminated or reduced
  - Workforce trained
  - New or enhanced technologies
  - New scientific approaches
  - Structural/behavioral/societal changes

All of the above are needed, but first scientific evidence is needed in early phase trials.

Strategy: What will it take to get there?

- Concrete actions to take in the next 1-5 years
  - RFAs to motivate the invention and testing of microdosing and monitoring devices (SBIR, etc), including the funding of Phase 0 neoadjuvant trials.
  - RFAs to evaluate organoids and other in vitro models (CTCs, CRCs) in a series of clinical trials.
  - RFAs for preclinical optimization of patient-derived cultures including organoids and other in vitro models for short-term drug sensitivity readouts and inclusion of stroma and immune cell infiltrates in culture conditions.
  - RFAs to 'platformize' patient-derived cultures and other in vitro models across large panels representing all types of cancer and including specific molecular subtypes, such that pre-screening of therapies can be done on a broad scale.
  - White paper on above that outlines the current limitations and opportunities.

What does success look like?

"Pharmaco-typing" our patient's tumors will complement the current genotyping efforts to understand and treat cancer patients. The ability to initially choose the most active therapies for cancer patients should optimize their care, and bring us closer to the treatment of bacterial infections. Furthermore, such approaches can be subsequently applied to address innate and acquired resistance to original therapies. In addition, databases populated with genotype and pharmacotype results from large numbers of patients can be mined for further predictions of of drug and drug combo sensitivity. Although not a primary goal, this effort could also expand the availability of preclinical organoid models for earlier stage screening of drug candidates.

Milestones per above:

1. Demonstrate that implantable microdosing/sensing devices can be safely tested in tumors in a Phase 0 neoadjuvant setting.
2. Determine whether tumor heterogeneity within a single tumor or between multiple tumors in a patient has the same sensitivity to therapeutics in a microdosing early phase trial.
3. Determine whether the most active therapies identified with implanted microdosing devices are predictive of patient clinical efficacy.
4. Demonstrate that organoids and other patient derived tissue models can be robustly generated from patients and genotyped and pharmacotyped in time frame that can influence prospective clinical management.
5. Determine whether organoids and other patient derived tissue models predict active therapies for patients.
6. Determine whether serial biopsies and organoid cultures can predict cancer heterogeneity, disease evolution, and therapeutic sensitivity and resistance.
7. Design clinical trials that can triage patients into treatment arms based upon the early results of a Phase 0 microdosing and organoid trials.

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