Case Comprehensive Cancer Center
Stanton L. Gerson, MD, Director
Cancer Moonshot Initiative
Observations, Recommendations and Suggested Focus Areas

March 30, 2016

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Case Comprehensive Cancer Center Executive Committee
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Background:

The Case Western Reserve University (CWRU) Comprehensive Cancer Center Executive Committee has been working under the guidance of Director Stan Gerson to develop recommendations to inform and guide the work of the Office of the Vice President to advance progress on cancer.

The Executive Committee brings together the Case Comprehensive Cancer Center (Case CCC) consortium partners – including University Hospitals (UH), Cleveland Clinic (CC), Case Western Reserve University (CWRU) and member MetroHealth System – in a collaborative effort to drive progress in cancer research and treatment for the benefit of the service population in northeastern Ohio.

In Northeast Ohio, the Case Comprehensive Cancer Center:
- Captures 2 out of every 3 oncology patients
- Enrolls almost 10% of patients in clinical trials

Set forth below are our observations and recommendations regarding the Cancer Moonshot which includes matters of national applicability, issues of particular impact in Northeastern Ohio, and opportunities related to particular areas of consortium expertise.

Many barriers exist in preventing expedited treatment solutions for cancer care. Included in those barriers are both infrastructure and political challenges.

Some of the key barriers include:
- The Veterans Administration as an independent system
- Low screening rates
- Low HPV vaccination rate
- Universal consent needs
- Poverty and access
- Environmental exposures
- Hospital competition
- Restricted data sharing

I. Recommendations:

A. Provide Support for Academic Cancer Center-based Drug Development Pipelines.

Case CCC investigators and their sponsor institutions (CWRU, UH and the Cleveland Clinic) have developed robust pipelines of new anti-cancer drugs that are in various stages of development -- ranging from chemistry to preclinical models to phase 1 and 2 clinical trials being conducted at consortium hospitals. We model new targets, mechanisms of treatment resistance, and novel drug combinations.

The National Cancer Institute (NCI), the institutions themselves, or philanthropic sources support funding for this pipeline activity. Currently, 17 drugs and 5 nano-therapeutics are in some stage of development. This model of development provides an environment where drug development can proceed in a cost efficient and objective manner focused on science and not one driven by commercial considerations.

Federal funding should be provided for this type of development model. In particular we have experienced a need for infrastructure resources to support early testing and modeling, and to support licensing to pharmaceutical and biotechnology entities.

3-year return (at Case CCC alone):

- 5 new cancer agents begin clinical trials after preclinical development and FDA review
- 3 new pathways of treatment resistance identified with treatment alternatives described

B. Support "Big Data" Integration Tools.

The Consortium partners have developed and implemented a solution to the big data sharing challenge. It is a single platform for secure clinical data from all major Cleveland hospitals – UH, CC, MetroHealth System, which together account for 70% of the 4.3M northern Ohio population -- including but not limited to EHR data, genomics, clinical outcomes and risk assessments.

All data is stored in a secure, HIPAA compliant CWRU managed database called the CLEveland Area Research Platform for Advancing Translational Healthcare (CLEARPATH) and

is available to any CWRU affiliated investigator under an overarching approved protocol; investigators may also request to re-identify individuals using their own individual approved protocol. CLEARPATH is scalable for all diseases and can easily include more hospitals and/or additional research networks.

In addition, Case CCC investigators have developed big data interrogation tools of electronic medical records that evaluate drug repurposing by finding which commonly used drugs are associated with improved outcomes in patients with cancer. A finding in ovarian cancers is now being evaluated in clinical trial.

3-year return:

- Review of the structure and impact of this big data initiative on research, patient care and quality assessments will benefit other centers and regions

II. Enhancing the quality and value of community based networks operated by major Cancer Centers:

A recognized need of the Moonshot effort is facilitating collaborations with researchers, doctors and patients to **overcome inconsistent care, excess cost, and poor outcomes**.

The American Association of Cancer Institutes (AACI) and the National Cancer Institute (NCI) Designated Cancer Centers represent approximately 92 Cancer Centers nationally. Through these centers and their regional community based networks, including care in rural areas, care for an estimated 700,000 patients with cancer occurs, representing over 40% of the entire country burden in newly diagnosed cancer patients.

By focusing efforts on coordinating care and emphasizing rapid introduction of new discoveries to patient benefit, through the AACI/NCI cancer centers, we could substantially affect the quality of care and outcomes for these patients.

This approach requires 3 main initiatives:

A. Coordinated Approach.

Through the AACI and NCI designated cancer centers, models of care (carepaths) can be agreed upon with strategy, infrastructure and business implication support. Consistent care will improve quality and outcomes, and reduce costs. While the National Cancer

Center Network (NCCN) guidelines are a consistent starting point, all major cancer centers are linking NCCN to diagnostic and treatment standards.

B. Quality Reporting.

Quality reporting is essential to understand the effect as well as drive compliance. Sharing EMR and databases are necessary to achieve this goal.

C. Clinical Trials.

Clinical trials provide access to novel drugs. To improve access across community networks we need to:

- Reduce barriers to enrollment
- Increase genomic and other special testing for marker-based treatment
- Develop clinical trials that are appropriate for regional sites to improve patient outcomes.

Attention to these approaches would enhance coordinated care, reduce competition, improve outcomes and manage costs.

III. Focus Areas

A. Recommended Focus Areas to Produce Substantial Results:

Case CCC is in support of the focus areas identified in the NCI budget justification, and the letter of support provided by the Association of American Cancer Institutes.

Based on our expertise, we have identified a number of topics of opportunity that pertain to the Moonshot's goal of significantly advancing progress on cancer. These topics fall under two areas of Consortium core competency – Screening and Prevention and Genomics.

Specifically, we identify topics where we would propose federal support for collaborative projects using coordinated clinical and research databases. These projects would accelerate, within 3 years, transfer of discoveries into meaningful impact on populations in areas of cancer screening, prevention, early detection, integrated care, personalized medicine and in specific areas of pediatric cancers, young adult cancers and drug discovery to clinical approval of more effective treatments for cancer.

- **Screening and Prevention**

The Cancer Moonshot should not solely focus on research and development related to treatments and cures, but also embrace the areas where immense progress can be made in reducing cancer incidence, including screening and prevention.

➢ **HPV Vaccination to Reduce Cervical and Head & Neck Cancers:**

Currently, only about 30% of boys and girls in the age range of 11-15 years old are being vaccinated for HPV. In Northeast Ohio, the Consortium partners have committed to developing programs to accelerate that vaccination rate toward a goal of 70% or higher.

What will be needed to drive this level of improvement (both here and in other communities) is support for:

- Population studies
- Development of messaging and public education programs that the HPV vaccine is a cancer vaccine (with dissemination of that message through primary care and pediatric offices and school-based education programs)
- Vaccination rate monitoring programs.

Case CCC's region-wide Pediatric Practice Based Research Network is ideally positioned to rapidly implement such an initiative with appropriate funding support. Community interest encouraging vaccination for all school-aged children should facilitate improvement in vaccination rates.

➢ **Lung and Colon Cancer Screening:**

The Cleveland area has high death rates from colon cancer and lung cancer, a problem that is most pronounced in our underserved African-American community where screening rates are low and smoking rates are 40% above the national average. Nationally, rates of lung cancer screening for high-risk populations (those over 50 years of age with a history of smoking for 30 years or more) are quite low (less than 30%). This significantly raises mortality rates resulting from late diagnosis of these cancers.

Similarly, great gains in prevention and treatment of colon cancer can be achieved through improvements in screening. Better deployment of low-cost lung cancer screening as well as potentially colon cancer DNA testing (a technique developed at

CWRU) as an alternative to colonoscopy can help with this improvement. UH and CC administer inexpensive CT screening programs for at-risk smokers and patient registries that allow for monitoring of follow-up.

Significant advances in prevention through screening could be promoted by federal support to:

- Evaluate whether a DNA test for colon cancer has better acceptance in the population than colonoscopy
- Offset costs of screening, database maintenance and follow-up
- Develop and evaluate new smoking cessation programs

Additionally, support for novel imaging techniques (e.g., MRI fingerprinting), and screening tests (e.g., DNA based blood and saliva testing) hold the promise of bringing novel technologies into broader use.

➢ **Esophageal Cancer Screening:**

Obesity and Barrett's Esophagus are associated with increased rates of esophageal carcinoma (EC). Given that there has not been a great deal of improvement in treatment, early detection of both Barrett's (to prevent the onset of cancer) and of EC (when still curable) is an important medical objective.

Case Comprehensive Cancer Center members have identified DNA changes detectable from a brushing of the esophagus with a very simple self-administered balloon swab that can collect a sample for DNA analysis from the lower esophagus in a matter of minutes.

Funding to support evaluation of this balloon brush as a tool for prevention and early detection in patients thought to have Barrett's associated reflux could rapidly establish a new method to reduce the risks and deaths of esophageal carcinoma.

➢ **Aspirin for Colorectal Cancer Prevention:**

Case CCC, with collaborators at Harvard, demonstrated the molecular basis for the daily use of aspirin to protect against colon cancer. We demonstrated that PGDH-15 is a risk stratification biomarker that predicts who will and who will not benefit from aspirin chemoprevention.

Population screening for PGDH-15 identify those (~50%) who benefit from aspirin, reducing the use for those without benefit, and is an example of personalized precision preventive medicine.

To capitalize on this advancement, funding is needed to initiate a multi-site population-based assessment screening and intervention trial that identifies who benefits from aspirin use with reduced incidence of colon cancer.

- **Exercise, Weight Reduction and Diet:**

It is well known that obesity is a major cause of heart disease, diabetes and metabolic syndrome. Less recognized is its profound effect on increasing risks of colon, endometrial, breast and ovarian cancers. Conversely, exercise reduces risks of recurrence for these cancers.

Programs to reduce obesity through exercise in children and young adults, and programs that increase exercise after the diagnosis of cancer can have a significant impact. The link between healthy foods and lower cancer incidence is also well established, and improving dietary health by attacking the problem of healthy food deserts in urban areas needs to be recognized as part of an anti-cancer strategy.

Case CCC has funded investigators evaluating obesity and cancer; studying exercise -- both in school age children as a primary cancer prevention method, and in cancer survivors (including the elderly) as it pertains to reoccurrence; with interventions to correct each of these risks for cancer.

An additional focus area has involved studying and removing healthy food deserts in our community, analyzing the intervention for improved health outcomes.

Funding is needed for education programs, skilled fitness trainers to implement and evaluate exercise interventions, and biomarker monitoring of the impact of exercise on cancer risk.

- **Translating Genomic Insights to Reduce Risk and Improve Treatment:**

  - **Adolescent and Young Adult Cancer Genomics:**

Advances in outcomes for patients with cancer aged 15-30 years lags behind both older and younger individuals and there is a lack of ongoing focus on research in cancers in this age group. Further understanding of the etiology and biology of Adolescent and Young Adult (AYA) cancer is necessary to make significant advances in this population.

Through philanthropic support, Case CCC has developed a scientific focus on the etiology and biology of AYA cancers -- with special attention from these young patients.

Federal funding should be directed to support genetic analysis and interpretation to identify both known and novel pathways leading to cancer in this age group.

- **Unique Genetic Causes of Cancer in African Americans:**

For the first time, Case CCC investigators have identified unique genetic changes responsible for colon cancers and for myelodysplastic syndrome and acute myelogenous leukemia in African Americans living in northern Ohio, including Cleveland.

This finding provides direct evidence that cancer treatments are inadequate for this population, since current FDA-approved treatments are oriented toward a different set of genetic changes seen in Caucasians.

Funding should be directed to validate these unique genetic and potential epigenetic changes in minority populations across the US, and to evaluate new screening and treatment paradigms for African Americans carrying these mutations in their tumors.

- **High Cancer Incidence in Families:**

There are many families with a very high incidence of cancer that cannot be tied to any commonly known genetic indicators (as the BRCA 1, 2 genes and breast cancer).

Case CCC, working through both UH and CCF, support high-risk cancer family clinics that are serving families with high rates of cancer, including by supporting extensive screening and genetic testing. This type of selection and extensive genomic analysis of complex cancer families is critical to determine risk and treatment options for these families.

Funding to continue to collect these family members across the two health systems and select complex cancer families for complete and extensive genomic and database analysis to uncover the genetic cause of cancer in that family is badly needed.

- **Cancer Recurrence and Metastasis:**

The greatest fear for any cancer patient is the word recurrence. Understanding the biology behind tumor metastasis, and spread to other organs remains critical to developing new methods of early detection and treatments.

In Cleveland, investigators are evaluating metastasis samples to understand their genetic abnormalities, in order to improve detection and treatment strategies.

Funding is needed to expand research in this area using patient derived samples that will represent a major advance when the causes and triggers are identified.

3-year return:

- Improved rates of cancer screening and HPV vaccination
- Identification of new genes associated with AYA cancers and cancers in families
- Validation of cancer risk genes in African Americans with colon cancer or AML/MDS with new diagnostic approaches and new therapies directed towards these genetic changes

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