The report was accepted at the March 6, 2019 CTAC Meeting.
INTRODUCTION

On September 19, 2012, the 112th Congress amended the Public Health Service Act by enacting the Recalcitrant Cancer Research Act (RCRA) of 2012 (Public Law 112-239, §1083). The legislation called upon the National Cancer Institute (NCI) to identify two or more recalcitrant cancers that have a five-year relative survival rate of less than 20 percent and cause more than 30,000 deaths per year in the United States and to develop scientific frameworks that will assist in making progress against these cancers. Pancreatic ductal adenocarcinoma (PDAC) was identified by NCI as a recalcitrant cancer as defined, with its five-year relative survival rate of less than 6 percent that translates into the loss of almost 40,000 lives per year. A report focused on the NCI’s scientific framework for PDAC was submitted to Congress in 2014 and posted on NCI’s website. NCI convened the Progress in PDAC Research Working Group (PDAC Progress WG), chaired by Dr. James Abbruzzese, Duke Cancer Institute, to advise NCI on the implementation progress of the initiatives outlined in the scientific framework. Working Group members represent the broad clinical and translational research and advocacy communities (Appendix 1).

This report summarizes the recent deliberations of the PDAC Progress WG which focused on research progress of the scientific initiatives to date and suggestions for future areas of scientific research. The PDAC Progress WG focused on the impact of the four 2014 Scientific initiatives on the following broad cross-cutting areas of research: 1) Biology (genomics/metabolomics/tumor biology); 2) Animal and Human Tissue Models; 3) Risk, Prevention, Screening, Diagnosis; and 4) Treatment. A fundamental objective was to address the continued scientific relevance of the 2014 scientific initiatives. Other issues considered were the appropriateness of the NCI’s overall research direction as well as research gaps and opportunities. In addition to current progress, the importance of future therapies and new methods and clinical strategies to advance the field were emphasized.

THE 2014 SCIENTIFIC INITIATIVES

The 2014 Scientific Framework for Pancreatic Ductal Adenocarcinoma provided the background, rationale and implementation plans for four initiatives to expand PDAC research. These initiatives are summarized below:

1. Development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes mellitus (DM) of recent onset
Understanding the clinical and biological characteristics of new onset diabetic patients who subsequently develop or have undiagnosed PDAC is important for defining risk factors for screening and early diagnosis efforts.

2. **Evaluate longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors**
   Identification of patients with the earliest stage PDAC or those who have precursor lesions (pancreatic intraepithelial neoplasia - PanIN-3 - and cystic neoplasms of the pancreas) that are likely to evolve into PDAC have the best chance of cure. More accurate and sensitive methods to identify the molecular alterations that characterize these early lesions and predict future malignant invasion are needed. Longitudinal screening protocols that collect specimens from early lesions from patients at high risk of developing PDAC are important for identifying markers of disease progression.

3. **New therapeutic approaches in immunotherapy**
   Validation of new immunotherapeutic and stromal targets as well as interventions for clinical testing in animals and human tissue models is important for the identification of new therapeutic approaches.

4. **Developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways**
   Mutant forms of KRAS are present in 95 percent of patients with PDAC and are thought to play a role in the initiation and maintenance of pancreatic carcinogenesis and resistance to therapy. Opportunities now exist, based on the structural biology of the KRAS molecule to make progress in targeting this pathway.

**ASSESSMENT OF RESEARCH PROGRESS**

In September 2018 over the course of several weeks, the Working Group divided into four subgroups; 1) Animal and Human Tissue Models, 2) Biology (genomics/metabolomics/tumor biology), 3) Risk, Prevention, Screening, Diagnosis, and 4) Treatment. These subgroups convened via webinars to discuss current pancreatic cancer research being conducted in relation to each of the 2014 scientific initiatives. A Working Group member was appointed to guide the assessment of the research progress for each subgroup. NCI provided the WG the following information about NIH-supported research:

- Abstracts for FY 2015 – FY2017 NCI-supported grant projects and subprojects coded to 25 percent or greater relevance to pancreatic cancer; NII grant projects identified as relevant to PDAC in one of the four initiatives in the scientific framework; related information from specific NCI programs and initiatives along with other NIH projects with relevance to pancreatic cancer retrieved from the NIH RePORTER database (Appendix 2).

- Publications supported by grants submitted in response to relevant Funding Opportunity Announcements; NCI CDP Pancreatic Cancer Detection Consortium (NCI-PAR 15-289), and NCI-NIDDK Joint FOAs Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers and Coordination and Data Management Center (RFA-DK-14-027/RFA-DK-14-028) (Appendix 3).

- A listing of all open NIH supported clinical trials as of February 2018 (Appendix 4).
The full Working Group convened via an in-person meeting in October 2018 (Appendix 5) to discuss progress, opportunities, and gaps within the current PDAC scientific framework portfolio. The overall impression was that the initiatives in the scientific framework were still relevant. While important developments have been made, further work is needed to identify patients at risk for developing PDAC, optimize data/tissue collection, identify biomarkers, and improve clinical trial accrual, efficiency and outcomes.

**SUMMARY OF PROGRESS**

**Topics**

* **Biomarkers, Early Detection, Screening Assessment**

  Updates on the Early Detection Research Network (EDRN), the Pancreatic Cancer Detection Consortium (PCDC), the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC), and the Consortium for Molecular Cellular Characterization of Screen-Detected Lesions (MCL) were presented. Two main areas were discussed; 1) evaluation of longitudinal screening protocols with new imaging biomarkers for patients at high-risk of PDAC and 2) studies of the biological relationship between PDAC and diabetes mellitus (DM) in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

  EDRN’s goal is to develop and validate biomarkers for diagnosis and prognosis of early-stage cancer. A panel of integrated biomarkers including proteins, autoantibodies, metabolites and miRNA has been created. A major consideration is the ability to identify those at high risk of pancreatic cancer from the many patients found to have cysts. Opportunities exist for collaboration in the development of reference sets and standardized protocols. A US-Japan collaboration of pancreatic cancer was formed for the development of plasma biomarkers for early detection in early-stage disease.

  **Consortium for the Study of Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Assessment**

  The CPDPC conducts clinical research on; 1) Chronic Pancreatitis (CP) (including those with recurrent acute pancreatitis), and 2) Pancreatic cancer and pancreatogenic or Type 3c Diabetes Mellitus (T3cDM) and their pathogenic interrelationships.

  The CPDPC is composed of working groups. The DM-PDAC working group cohort study is collecting biosamples from diabetes patients to 1) establish a new onset diabetes (NOD) cohort, 2) estimate the probability of PDAC in the NOD cohort, and 3) validate biomarkers and develop early detection screening protocols. The goal of the NOD studies is to detect pancreatic cancer at an early and potentially curable stage and identify high risk groups for prevention. Several other studies are also underway. The Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study is testing whether pancreatic polypeptides will provide valid biomarkers to identify and distinguish T3cDM from T2DM. The adult Chronic Pancreatitis (CP) working group is establishing a cohort for study of CP and its complications. The pediatric study (INSPIRE2) will collect data from subjects with recurrent acute pancreatitis and chronic pancreatitis to evaluate risk factors, time frame for progression to CP, and characterize this cohort.

  **Moonshot (Immunotherapy and Microenvironment) Pancreatic Cancer Microenvironment Network (PaCMEN) Assessment**

  PDAC Progress WG Report: Accepted by the Clinical Trials and Translational Research Advisory Committee on March 6, 2019 (as of 3-8-2019)
An update on the PaCMEN was provided. The purpose of the network is to stimulate research on the PDAC microenvironment with the goal of understanding the interaction between tumors and the microenvironment to design new immunotherapy and other treatment interventions. PaCMEN has advanced the study of the immunogenicity of pancreatic cancer. New evidence suggests the ability to reprogram the tumor microenvironment, making it more amenable to immunotherapy.

The development of resource centers with a multidisciplinary team approach and research projects focused on 1) dissecting multi-cellular heterogeneity, 2) disrupting the immune and drug privileged microenvironment, 3) defining neoantigen immunodominance and quality for biomarker and target discovery, 4) interrupting cellular cross-talk and 5) reprogramming the PDAC tumor environment which could lead to the success of this program.

**RAS Initiative Assessment**

The major goals are to discover small molecules that bind to RAS directly or disrupt RAS/effector interactions, and to molecularly describe the RAS/RAF signaling complexes in the membranes. The RAS Initiative follows a *hub and spoke* model for collaboration with academia, industry and other partners. Cooperative research and development agreements with private companies have amplified initiatives and efforts. RAS resources can be distributed worldwide.

Developing and understanding of the structural components of RAS is a priority; new targetable pockets and configurations in oncogenic RAS mutants have been identified. The specific aim of the RAS Initiative is to find molecules that target RAS. Once molecules that bind RAS have been identified they will be studied in PDAC. The initiative is interested in using cell lines derived from pancreatic cancer, but the overall initiative goal is to find molecules that bind to wild type and mutant RAS.

The RAS Synthetic Lethality Network (SLN) has been up and running for two years. Groups are starting to generate a list of targets and are comparing lists to cross validate the targets. The challenge will be to evaluate the output and determine overlap, and to validate those findings.

An important experimental gap is the pathway to activation of RAS. The RAS Initiative has been consolidated to 1) direct targeting of KRAS and 2) understanding the biology in the context of the plasma membrane. Novel classes of compounds to target KRAS have been identified. Partnering with biopharmaceutical companies (Pharma) and NIH is needed to screen leads and move candidates toward the clinic.

**Discussion**

The PDAC Progress Working Group agreed that NCI-funded initiatives have been useful for advancing research. Sustaining funding is an important consideration. Additional high quality molecular studies will provide evidence of efficacy to engage Pharma in PDAC research and will provide important collaborative opportunities to expand research initiatives. There was a consensus that early detection alone is not sufficient because even at an early stage, patients may have metastatic disease. All agree that novel techniques and approaches are needed to treat PDAC.

Grant mechanisms to create academic-industrial partnerships to validate and move technical developments into the clinic are in place. This is a welcomed development as it is important to partner to make real progress. A new consortium has been developed for industry-academic partnerships to
study liquid biopsies and biomarkers. The established consortia are an enormous resource. However, the Working Group felt that representatives from Pharma at the consortia meetings would be beneficial and that facilitation by NIH would be of value.

For early detection, CPCDC is a clinical consortium that the Working Group felt was missing a basic science component. Instead of recasting the consortia every five years, perhaps basic scientists need to be encouraged to interact with the consortia via the use of investigator-initiated projects to stimulate creativity. To move forward with discovery broad areas of expertise are needed. Additionally, the Working Group reminded NCI that even if biomarkers for early detection are validated, there is a huge educational component to get them into the community setting.

New clinical studies, programs and collaborations are underway including plasma biomarkers studies for early stage disease, surveillance methods for distinguishing precancerous and cancer lesions and creation of annotated tissue banks for in-depth study of the molecular basis of disease. The RAS Initiative was highlighted with a focus on direct targeting of allele specific RAS/KRAS and understanding of its structure, biology, and interactions within the plasma membrane. The PaCMEN has advanced immunotherapy options as part of the Moonshot initiative, while the CPDPC has initiated both adult and pediatric studies for evaluating pancreatitis and establishing a new onset diabetes cohort.

**PDAC BIOLOGY- GENOMICS/METABOLOMICS/TUMOR BIOLOGY**

**Assessment**

There is a need to better understand systemic and local metabolic perturbations, and the effect of the microbiome and the intratumoral microbiome that underlies the diabetes axis and its relationship to cachexia. NCI Moonshot has pioneered new therapy approaches in immunotherapy. RAS remains central to PDAC with the NCI RAS Initiative as a primary effort and RAS SLN as a secondary. Scientific gaps for new opportunities exist in the areas of genomics, metabolomics, tumor biology and immunology. Considerations include oncogenic drivers, biology of RAS variants, KRAS effect on metabolism, tumor evolution, and the tumor microenvironment. Circumventing bypass signaling pathways and understanding of the role of the stromal elements of the tumor microenvironment remains critical.

Better correlative studies will provide information on study failures and exceptional responders. Risk prevention, screening, and diagnosis are the basis for future model systems. A well-annotated biorepository, and refined screening and assay criteria are necessary for therapeutic advances in this disease. Imaging, screening, and integration of biomarkers are all essential for clinical advancement.

**Research Gaps and Opportunities**

- New methodologies to improve the feasibility of obtaining serial biopsies will increase research options
- The role of the pancreas in regulating nutrition and metabolism and the biological mechanisms of PDAC associated cachexia
- How PDAC evolves in response to treatment and the biological mechanism of treatment resistance
- The role of stroma in the disease process
• Identification of targets that bind RAS in diseases of the pancreas

Discussion
NCI has been responsive; however, continuous efforts are needed to move the field forward. Endocrine/exocrine factors, early detection, and the importance of therapy to those at risk was highlighted.

With NOD as a marker for disease, looking at glycemic control 7-8 years prior to pancreatic cancer diagnosis is critical. There is some evidence that hyperinsulinemia leading to poor glycemic control and PDAC are related. Metabolism studies need to be included and expanded. For early detection, stage I and II is too late for pancreatic cancer. Focusing on developing more sensitive methodologies is important for the earliest detection.

Systemic and local metabolic perturbations, and the effect of the microbiome and the intertumoral microbiome, are an area of emerging exploration. The biophysics of the pancreas and PDAC are unique. Stromal progression models are needed since the biophysical properties of the pancreas change with tumor progression. This area of research will aid in the identification of dependent therapeutic products. Additionally, the current treatment system can be enhanced by the addition of in vivo imaging and investment in agents that can image drug delivery. In vivo imaging can also be helpful to study the biomechanics and fluid mechanics of the tumors.

A more thorough understanding of the biology of tumor progression is needed. There are sophisticated methods to analyze the cellular composition of tissue that can be used to analyze pancreatic cancer versus chronic pancreatitis. Research in locally advanced disease and metastatic lesions that occur very early in the disease process need further study. Longitudinal sampling across different stages of disease will provide opportunities important for this type of research.

The science coming out of the RAS Initiative is extraordinary. However, more emphasis on RAS mutations in pancreatic cancer is desired as mutation of KRAS appears to be an initiating event in this disease. Different specific RAS mutations may have different downstream effectors, emphasizing the need for a more directed effort in this space.

ANIMAL AND HUMAN TISSUE MODELS

Assessment
There have been tremendous advances in mouse and organoid model systems over the past several years. Animal and human tissue models remain an important component to PDAC related research. They are useful for cause and effect studies of mutant genes. Mouse models showed that the KRAS mutation is an initiating event in PDAC. The KPC mouse is a useful model that develops invasive ductal disease. In this mouse model KPC stands for: Kras, p53, and Cre. Kras and p53 are two genes that are often mutated in human pancreatic tumors. Cre is a special tool gene that is used to control where Kras and p53 are turned on. Mouse models that specifically allow for a deeper understanding of the transition from high grade PanIN to invasive cancer are an unmet need, as are models of pancreatitis and DM.
Organoids, artificially grown masses of cells or tissue that resemble tumors can be made from human or mouse cancer cells. They may serve well in biomarker discovery, drug testing, and in the study of biological properties of cancer. For organoid pancreatic model systems, there are no reports of model comparisons, including success rates and validation to the primary tumor. Modified and non-epidermal growth factor/Noggin/R-spondin1 (ENR) organoids need comparison and validation to be used for therapeutic modeling. Organoid models provide stromal cultures for biological medicine applications. A comprehensive analysis of the extracellular matrix is needed as are more efficient ways of disseminating organoids.

The further development of additional models of pancreatitis, diabetes, obesity, genetic deficiency and metastasis are relevant to PDAC research. Additional studies of high grade PanIN and focal PDAC, imaging, and liquid biomarkers are also critical. A well annotated mouse tissue resource will be beneficial to the field.

Research Gaps and Opportunities

- Mouse models of high grade PanIN, pancreatitis and DM that recapitulate human disease
- Collection and interrogation of samples from exceptional responders and non-responders
- Better models of metastatic disease
- Combining models of cachexia with models of PDAC

Discussion

NCI has initiatives and programs to help stimulate research in PDAC animal and human tissue model systems. The NCI PDM (Patient Derived Models) repository (pdmr.cancer.gov) contains cell lines, and organoids available to extramural scientists. The tissue samples are sequenced, many associated with a clinical history. Additionally, the NCI supported Rapid Autopsy program has been collecting samples and is developing SOPs for both the collection and shipping of fresh tissue, which can be made available.

RISK, PREVENTION, SCREENING, DIAGNOSIS

Assessment

In prevention and diagnosis, progress has been made in understanding risk and prevention of pancreatic cancer such as: IPMN classification, and the genetics of cysts and molecular testing. Improved study design and larger validation cohorts are needed to further elucidate risk and prevention. Screening to identify high risk individuals will aid in detection of early stage disease. There is an effort to have more ethnic and racial minority representation in clinical trials and understand potential genetic differences and similarities. To date studies in minority populations have identified a higher incidence of the CD2K mutation. These studies need to be continued.

Research Gaps and Opportunities

- Artificial intelligence/machine learning
- Integration of blood-based biomarkers
- Delivery of genetic testing/counseling to patients and relatives
- Development of vaccines for PDAC prevention
• Relationship between the microbiome and increasing rates of obesity and DM
• Knowledge of the relationship between obesity and Maturity Onset Diabetes in the Young (MODY) as risk factors for pancreatic cancer
• Identification of high-risk patients in those with pancreatic cysts

Discussion
Education initiatives include identification of at-risk patients, education on diagnosis and treatment, and expanding knowledge of pancreatic diseases. Methods to capture the patient population lacking a family history need to be investigated. Detection of patients who have sporadic risk will have the greatest impact.

Computer science and molecular imaging have made great strides. Revolutionary changes will occur when we can evaluate the molecular characteristics through imaging. The nature of surveillance, physical exam versus imaging, plays a role in the ability to identify lesions and progression in pancreatic cancer. Use of ultrasonic and optoacoustic methods for diagnosis hold promise but will need continued support. There are opportunities to do screening trials utilizing imaging technologies. There are currently microbubble agents that can be used with hand-held ultrasound detectors—a technology that is exciting and promising. Optoacoustic imaging is being developed which might be of use in imaging of PDAC related lesions. These will need additional technological development along with the development of diagnostic drugs. Radiomics and machine learning with sophisticated imaging analyses are possibilities of the near future.

The relationship between obesity and inflammation, and the recognition that obesity is a significant risk factor for pancreatic cancer was highlighted. It is a difficult area to study but is thought to be critically important in sporadic pancreatic cancer. Epidemiological studies have shown with bariatric surgery patients, only some of them are diabetic, but research implies they have insulin resistance. After bariatric surgery the incidence of pancreatic cancer is cut in half and insulin levels return to normal. This implies that insulin might be an active player in pancreatic cancer. The estimated proportion of pancreatic cancer incidence attributable to overweight and obesity in the US is 15 to 20 percent. This proportion is greater than the proportion estimated to be attributable to smoking or genetic susceptibility given the current high prevalence of overweight and obesity (71.6 percent) in the US adult population. Therefore, overweight and obesity is important to understand as risk factors for pancreatic cancer. In view of the current obesity epidemic in this country, the Working Group felt that NIH investment in obesity research and the link between obesity, DM, and PDAC is important.

A high priority is to bring together centers that have a large number of genetically tested and high-risk patients. For high-risk individuals, the question of how often to collect samples is critical; currently, there are no standards. We need to educate physicians and patients with convincing evidence. Our best chance of having patients survive PDAC is the identification of pre-invasive disease. We need to understand better the relationship between pancreatitis, obesity, glucose intolerance, and diabetes. Competing tissue needs for limited samples is a challenge in the use of diagnostic biopsies; development of new methodologies that use smaller quantities of tissue is critical.

TREATMENT
Assessment
An update on progress in the treatment of PDAC was provided. Updates on modalities, management of disease states, and horizon opportunities were discussed.

Improvement in treatment methods have included enhanced surgical and laparoscopic techniques resulting in reduced morbidity, improved risk/benefit determination and enhanced patient quality of life (QOL). However, for most patients, systemic therapy for PDAC has not improved outcomes significantly and there is urgency on the part of patients, families, and oncologists that expedited efforts are needed to expand therapies beyond traditional cytotoxic chemotherapy approaches. The importance of new therapies is underscored by its inclusion in two points of the scientific framework.

Over the past 5 years surgical improvements have resulted in a reduction in morbidity and mortality allowing more surgical intervention within quality centers of expertise. Other therapies including radiation, endoscopic ultrasound, and systemic therapy have had improvements in technique for better patient selection, diagnosis, reduced morbidity and improved QOL. Progress has been made in resectable and borderline disease allowing for management of micro-metastatic disease and a decrease in R1 resection rates. Promising results have been seen for 6-months treatment with adjuvant FOLFIRINOX (a combination of chemotherapeutic agents; leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin) following resection. However, patient selection and chemotherapy tolerance remain a concern. Although systemic therapy is used to prevent disease recurrence, there is still a problem with local control. Advances in surgical techniques and radiotherapy may help to limit local disease progression.

Future objectives discussed included novel treatment strategies and precision medicine for mutant KRAS tumors, and more rapid return of molecular analysis for clinical decision-making. Patients should not wait more than 10 days to begin treatment. Improved understanding of cachexia and sarcopenia, immunotherapy, and the microenvironment are necessary for the design of future treatment strategies.

Focus on development of endpoints and statistics relevant to pancreatic cancer clinical trials is important for the design of future clinical trials. Current clinical trial designs do not take into the account the aggressiveness of the disease, making accrual to PDAC trials difficult.

Further, the high symptom burden faced by many patients with PDAC warrants additional research into improving palliative and supportive care, optimizing pain management, and improving care of patients at the end of life.

Research Gaps and Opportunities
- Treatments other than cytotoxic chemotherapy
- Advances in precision medicine
- Opportunities to learn from clinical trial failures
- Consensus on endoscopy methods
- Methods to improve palliative and supportive care including optimization of pain management and end-of-life care

Discussion
For tissue acquisition, there is no clear consensus on protocols. Assembling a working group to look at how best to obtain tissues is of great interest. An organized, systemized approach would be helpful. There is a shortage of effective systemic treatments. Only 5 percent of patients are going on trials; how can we encourage patients to go on trials? Are we over-selecting patients, such as those with the most aggressive disease? Are inclusion criteria too restrictive and perhaps irrelevant to the treatment?

Any biomarkers that signal disease would need to be followed up by biopsy unless we have better imaging. One third of patients will die with a component of local disease, so local disease is important to study. The potential for radioimmunotherapy is very exciting in PDAC.

An area of imaging to further explore is after neoadjuvant therapy. Understanding characteristics of tumors after neoadjuvant therapy would help determine the difference between fibrosis and disease progression. If imaging is going to be important, we need better pancreatic-specific treatments and more specific imaging markers.

RESEARCH GAPS AND OPPORTUNITIES

RESEARCH GAPS

- Biological relationship between PDAC and metabolic disruptions, including diabetes, obesity, cachexia and sarcopenia
- The relationship between diabetes and PDAC in minority/underserved populations
- Recapitulating the relationship between PDAC, diabetes, and insulin metabolism in animal models
- Intratumoral heterogeneity
- New therapies
- New statistical approached and methodologies to clinical trial designs for rare and aggressive cancers
- Clinical trial accrual issues; barriers to trial entry, inclusion/exclusion criteria, and trial design issues

RESEARCH OPPORTUNITIES

PDAC Biology- Genetics/Metabolomics/Tumor Biology

- Perturbations of the tumor microenvironment and its impact on tumor progression and therapeutic response
- Understanding the role of the microbiome
- Greater understanding of PDAC disruption of metabolic pathways
- The role tumor cell heterogeneity plays in drug resistance

Animal and Human Tissue Models

- Mouse models of high grade PanIN, pancreatitis, and DM that recapitulate human disease
- Use of organoids as pre-clinical and co-clinical platforms for biomarker discovery and therapeutic prediction
- Complementary strategies to model the disease as a whole
- Collection and interrogation of samples from exceptional responders and non-responders
Risk, Prevention, Screening, Diagnosis

- Development and validation of biomarkers for detection of sporadic early stage pancreatic cancer
- Integration of imaging methods with screening and biomarkers
- Artificial intelligence/machine learning to integrate different biomarkers, i.e., cell-free DNA, blood-based genetic susceptibility markers
- Enhanced delivery of genetic testing to patients and relatives
- Education initiatives to identify at-risk patients, improve diagnosis, and accelerate and expand treatment opportunities

Treatment

- Improvements to immune therapy including capitalizing on resource centers and diverse scientific expertise, addressing multi-cellular heterogeneity, disrupting drug privileged sites
- Improving the integration of radiation therapy with immunotherapy, targeted therapies, and chemotherapy for resectable and locally advanced disease
- Determining the impact of chemotherapy on the immune system and immunotherapy
- Partnerships with biotech, Pharma, and NIH to more rapidly screen for lead compounds and collaboration for the development of reference sets and standardized protocols
- New treatment methods for pancreatic cancer especially metastatic disease
- Innovative designs to address challenges with pancreatic clinical trials
- Precision medicine, serial biopsy, and longitudinal assessments
- Strategies to enhance clinical trial accrual
- Standards for clinical data and tissue acquisition
- Clinical trials with longitudinal biospecimen collection
- Improvements in palliative, supportive, and end-of-life care

CONCLUSIONS AND NEXT STEPS

The 2014 Initiatives are still relevant and vital to continued progress.

The Group agreed while significant progress has been made the initiatives identify key areas for continued focus. NCI has been responsive in developing new approaches and initiatives in diverse research areas including molecular targets, risk factors, and immunotherapy. However, continued efforts and continued evolution of research methods are needed to move the field forward.

Although progress has been made in understanding risk factors of pancreatic cancer new study designs and larger validation cohorts are needed to further identify individuals at risk. Methodologies to detect patients who have sporadic risk will have the greatest impact on outcomes. Epidemiologic studies suggest that 15-20 percent of pancreatic cancers are attributable to overweight and obesity. Alterations of metabolic processes that occur because of diabetes are better understood than the unusual disruption of metabolic processes that occur as a result of pancreatic cancer. Understanding the metabolic perturbation will aid in the development of prevention activities (lifestyle alterations) and treatment decisions that often must be made in the setting of diabetes, cachexia, and sarcopenia due to
advanced disease. The relationship between the microbiome, obesity, and diabetes, although difficult to study will provide opportunities for improving outcomes for patients at risk of developing pancreatic cancer.

Clinically, a fundamental change is needed in treatment approaches that can offer better therapies and patient care in this recalcitrant disease. There is a history of trial failures that needs to be evaluated and addressed to create change in pancreatic cancer therapeutics. In addition, maintaining a patient centered research design and optimizing palliative and supportive care while incorporating new techniques and assessing patient benefit will optimize study impact and patient outcomes.

Specific tissue collection methods, better quantitation of available biopsy material, and standardization across the field are modifications that can benefit clinical research efforts. Incorporating new technology such as organoids and animal models that better recapitulate the human disease will provide opportunities for increased efficiency and reproducibility. Likewise, barriers to trial entry including strict eligibility and organ function criteria need be re-evaluated and amended to increase patient enrollment since many patients have co-morbidities. Expanding and diversifying the patient population that is eligible to participate in trials will enhance research in this disease.

APPENDICES - SUPPLEMENTAL RESOURCES

Appendix 1: Progress in Pancreatic Ductal Adenocarcinoma (PDAC) Research Working Group (PDAC Progress WG) 2018 Roster

Appendix 2: Funded Project Summary FY 2015 – FY2017
- NIH PDAC Funded Projects, Initiative 1: Understanding the Biological Relationship Between PDAC and Diabetes Mellitus
- NIH PDAC Funded Projects, Initiative 2: Evaluating Longitudinal Screening Protocols for Biomarkers for Early Detection of PDAC and its Precursors
- NIH PDAC Funded Projects, Initiative 3: Studying New Therapeutic Strategies in Immunotherapy
- NIH PDAC Funded Projects, Initiative 4: Developing New Treatment Approaches that Interfere with RAS Oncogene-Dependent Signaling Pathways
- NIH PDAC Funded Projects, not related to the Framework Initiatives

Appendix 3: PDAC Publications Supported by Grants Submitted in Response to Funding Announcements
- NCI-PAR 15-289: NCI CDP Pancreatic Cancer Detection Consortium
- RFA-DK-14-027 and RFA-DK-14-028: NCI-NIDDK Joint FOAs Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer Clinical Centers and Coordination and Data Management Center

Appendix 4: Open NCI PDAC Supported Clinical Trials as of February 2018

Appendix 5: NCI Clinical Trials and Translational Research Advisory Committee (CTAC) Progress in Pancreatic Ductal Adenocarcinoma Research Working Group (PDAC Progress WG) October 17, 2018 Meeting Agenda

PDAC Progress WG Report: Accepted by the Clinical Trials and Translational Research Advisory Committee on March 6, 2019 (as of 3-8-2019)