Thank you for the opportunity to provide public comment on the FDA’s patient-focused drug development initiative. In reviewing the preliminary list of disease areas identified, we feel an important disease category has been omitted from the nominations—hereditary cancer syndromes caused by high-penetrant mutations.

We are submitting commentary on behalf of Facing Our Risk of Cancer Empowered, also known as FORCE, which represents nearly a million people living with a BRCA genetic mutation in the U.S. We are also representing populations affected by Lynch Syndrome, Cowden Syndrome, Fanconi Anemia, Ataxia Telangiectasia, Li Fraumeni, and other hereditary cancer communities. Altogether, it is estimated that hereditary cancer syndromes affect over 2 million Americans.

Women who have a BRCA genetic mutation face up to an 85% chance of developing breast cancer and as much as a 60% chance of ovarian cancer in their lifetime. BRCA mutation carriers are also at higher than average risk of melanoma, prostate, pancreatic and male breast cancers. Women with a BRCA mutation are 5 times more likely than women without hereditary cancer to be diagnosed with cancer in the opposite breast.

Affecting more than 600,000 or one in 370 people in the U.S., Lynch Syndrome or hereditary nonpolyposis colon cancer (HNPCC) is the leading hereditary cause of colon and uterine cancers. HNPCC imparts a lifetime colon cancer risk of up to 80%. It also causes a lifetime risk of as much as 60% for endometrial and 12% for ovarian cancers. Recently, a handful of international studies have indicated that this community also presents with a subset of breast cancer reflecting an eight-fold risk to the affected. An increased risk of a myriad of other cancers also exists, including stomach, pancreas, kidney, prostate, ovarian, brain, and more. The average age of onset of these cancers is often decades before the general population.

Cowden Syndrome most commonly results from a mutation in the PTEN gene. Mutations in PTEN confer up to a 50% lifetime risk for breast cancer and a 10% risk of thyroid and endometrial cancers. Reports of several other types of malignancies exist, including colon cancer and renal cell carcinoma. Ataxia Telangiectasia is an inherited disease causing severe disability. Unfortunately, approximately 20% of A-T patients develop some sort of cancer in their lifetimes—usually lymphoreticular cancers like leukemia or lymphoma. Fanconi anemia, or FA, is primarily a blood disease which may affect all body
systems, but it is also a cancer-prone disease. Patients with FA are hundreds- to thousands-fold more likely to develop specific solid tumors at unusually young ages, including squamous cell and breast cancers. Of the 15 FA genes identified, 4 of the genes are recognized as breast cancer susceptibility genes. Li-Fraumeni Syndrome also greatly increases susceptibility to cancer. Persons with Li–Fraumeni Syndrome have an approximately 25-fold increased risk of developing a malignant tumor by age 50, and are at risk for a wide range of malignancies, with high occurrences of breast cancer, brain tumors, acute leukemia, adrenal cortical carcinoma, and soft tissue and bone sarcomas.

Hereditary cancer treatment and pharmacoprevention offer unique opportunities for exploiting the known gene defects and associated genes to develop population-specific treatments and preventions. However, they also offer distinct challenges including the fact that hereditary cancers are rarer and consist of a smaller subset of the larger cancer cohort. As such:

- There are fewer financial incentives for pharmaceutical companies to target these cancers vs. the larger disease population.
- Patients with hereditary cancer are motivated to participate in clinical trials and registries. However, they often enroll in studies that focus on sporadic cancers because of the number and availability of these larger, less targeted studies. This leads to a vicious cycle where fewer pharmaceutical companies are willing to develop drugs due to recruitment challenges.
- Tests to identify and define members of hereditary cancer populations create their own challenges to therapeutic development because they are often expensive, lack FDA approval or simply aren’t utilized.

Nevertheless, it is important to develop new preventive and therapeutic agents for those with inherited cancer because of their unique challenges:

- The lifetime risk for familial cancer is significantly higher, and cancers often strike younger and are more aggressive than sporadic cancers. This may lead to a different risk-benefit ratio for prevention and treatment than for sporadic cancers.
- The genes and pathways associated with these cancers are frequently known, lending the opportunity to target vulnerabilities that may not exist for sporadic cancer.
- Hereditary gene mutations are sometimes associated with different risks and benefits for therapeutic agents compared with published standard-of-care for sporadic cancers. Much more needs to be learned about “standard therapy” in these specific populations and how to develop protocols that don’t expose patients to increased harm.

For example:
- BRCA mutation carriers may be more sensitive to the heart damaging effects of Adriamycin, a standard breast cancer chemotherapy agent;
- 5-FU, a mainstay of standard chemotherapy for colon cancer, works only for some patients with Lynch Syndrome;
People with Li Fraumeni may be more sensitive to radiation therapy; and
Individuals with Ataxia-Telangiectasia cannot receive standard radiation or chemotherapy because they are extremely sensitive to the cytotoxic effects associated with these therapies.

- Currently, risk-management for hereditary cancer syndromes focuses on cancer screening and surgical interventions. Many inherited cancers, including ovarian and pancreatic cancer, have no good early detection and a high mortality rate. Development of drugs explicitly to prevent cancers in individuals with hereditary cancer syndromes is achievable and could save thousands of lives and dollars per year.

- Cancer is increasingly understood as a heterogeneous group of diseases whose molecular signatures likely determine prognosis and response to therapy. The next generation of cancer therapies is expected to target these molecular changes. Hereditary cancer syndromes provide a scientifically unique opportunity to develop targeted therapies, paving the way for next generation diagnostics and therapies that will be applicable to the broader cancer community.

PARP inhibitor research, and the challenges in developing this class of drugs for those with BRCA mutations, offers an example of why it is crucial for hereditary cancers to be considered a unique condition for patient-focused drug development.

- PARP inhibitors are a class of drugs developed specifically to treat hereditary cancers. Early studies on BRCA mutation patients suggested that they are an effective therapy in this population.
- Despite this, pharmaceutical companies have focused on larger communities less likely to benefit from these drugs.
- FDA registration trials using PARP inhibitors have focused on sporadic ovarian or triple negative breast cancer rather than BRCA-associated cancers. As a result, the trials have not met primary endpoints.
- Further complicating matters, the FDA does not recognize BRCA testing as a companion diagnostic for the development of targeted therapy or subsequent drug labeling.
- Some pharmaceutical companies have abandoned PARP inhibitor research due to these challenges, and others are threatening to do the same.

BRCA mutation carriers are not the only patients who stand to benefit from this class of drugs. At least two studies suggest that PARP inhibitors may be effective in treating ATM deficient cancers as well.

The issues at stake here have clear implications beyond drug development for those affected by hereditary cancer, including much broader issues related to the translation of basic science findings into personalized medical therapies based on genetic predisposition to disease. With the increasing availability of whole genome sequencing these issues will continue to arise with increasing frequency.
These identifiable subpopulations within the broader cancer community are profoundly impacted by their high risk for multiple cancers—cancers that often strike younger, and are more aggressive than sporadic cancer. Few, if any, clinical trials appropriately address the needs of this population and there are currently no therapies available that target the distinctive traits of these syndromes. We urge the FDA to add hereditary cancer syndromes to the list of disease priorities in the patient-focused drug development initiative. The hereditary cancer community bears a heavy cancer burden. It’s time to remedy this disparity while optimizing the promise of personalized medicine.

FORCE: Facing Our Risk of Cancer Empowered
Colon Cancer Alliance for Research and Education for Lynch Syndrome
Fanconi Anemia Research Fund
PTEN World
Lynch Syndrome Screening Network
A-T Children’s Project

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The Ataxia Telangiectasia Mutated (ATM) gene is frequently inactivated in lymphoid malignancies such as chronic lymphocytic leukemia (CLL), T-prolymphocytic leukemia (T-PLL), and mantle cell lymphoma (MCL) and is associated with defective apoptosis in response to alkylating agents and purine analogues. ATM mutant cells exhibit impaired DNA double strand break repair. Poly (ADP-ribose) polymerase (PARP) inhibition that imposes the requirement for DNA double strand break repair should selectively sensitize ATM-deficient tumor cells to killing. We investigated in vitro sensitivity to the poly (ADP-ribose) polymerase inhibitor olaparib (AZD2281) of 5 ATM mutant lymphoblastoid cell lines (LCL), an ATM mutant MCL cell line, an ATM knockdown PGA CLL cell line, and 9 ATM-deficient primary CLLs induced to cycle and observed differential killing compared with ATM wildtype counterparts. Pharmacologic inhibition of ATM and ATM knockdown confirmed the effect was ATM-dependent and mediated through mitotic catastrophe independently of apoptosis. A nonobese diabetic/severe combined immunodeficient (NOD/SCID) murine xenograft model of an ATM mutant MCL cell line demonstrated significantly reduced tumor load and an increase-survival of animals after olaparib treatment in vivo. Addition of olaparib sensitized ATM null tumor cells to DNA-damaging agents. We suggest that olaparib would be an appropriate agent for treating refractory ATM mutant lymphoid tumors.


Poly(ADP-ribose) polymerase-1 (PARP-1) inhibition is toxic to cells with mutations in the breast and ovarian cancer susceptibility genes BRCA1 or BRCA2, a concept termed synthetic lethality. However, whether this approach is applicable to other human cancers with defects in other DNA repair genes has yet to be determined. The ataxia telangiectasia mutated (ATM) gene is altered in several human cancers including mantle cell lymphoma (MCL). Here, we characterize a panel of MCL cell lines for ATM status and function and investigate the potential for synthetic lethality in MCL in the presence of small-molecule inhibitors of PARP-1. We show that Granta-519 and UPN2 cells have low levels of ATM protein, are defective in DNA damage-induced ATM-dependent signaling, are radiation sensitive, and have cell cycle checkpoint defects: all characteristics of defective ATM function. Significantly, Granta-519 and UPN2 cells were more sensitive to PARP-1 inhibition than were the ATM-proficient MCL cell lines examined. Furthermore, the PARP-1 inhibitor olaparib (known previously as AZD2281/KU-0059436) significantly decreased tumor growth and increased overall survival in mice bearing s.c. xenografts of ATM-deficient Granta-519 cells while producing only a modest effect on overall survival of mice bearing xenografts of the ATM-proficient cell line, Z138. Thus, PARP inhibitors have therapeutic potential in the treatment of MCL, and the concept of synthetic lethality extends to human cancers with ATM alterations.