Published in final edited form as:

Pediatr Blood Cancer. 2013 June ; 60(6): 955–956. doi:10.1002/pbc.24399.

The Children's Oncology Group's 2013 Five Year Blueprint for Research

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Since the introduction of chemotherapy for the treatment of childhood leukemia more than 50 years ago [1], the prognosis of childhood cancer has improved dramatically. The 5-year survival rate for childhood cancers, many of which were uniformly fatal in the pre-chemotherapy era, was 80% for all forms of childhood cancer diagnosed between 1996 and 2004 [2]. Despite these advances, several childhood cancers still have unacceptably low cure rates [3], and even when treatment is successful, the acute and long-term morbidity of current therapy can be substantial [4,5]. For several decades, the overarching strategic approach for most childhood cancer treatment has been an intensification of therapy for select subpopulations of children [6]. In general and especially for children with non-hematologic malignancies, the approach is no longer yielding meaningful improvements in survival [7]. The development of new therapeutic approaches must be a priority for childhood cancer basic, translational and clinical researchers.

We are entering an era of an unprecedented pace of discovery in cancer research. Costs associated with whole genome sequencing and related methods are falling precipitously [8], and thus our ability to understand the molecular basis of a spectrum of childhood cancers is potentially within reach in a timeframe unimaginable just 5 years ago. We should anticipate that a number of molecular targets will be defined for which there are therapeutic approaches currently available or in clinical development for adult cancers. The key question will shift from the laboratory back to the bedside as we ask how we will leverage this knowledge into an improved outcome for children with cancer.

The Children's Oncology Group (COG), the world's largest organization devoted exclusively to childhood and adolescent cancer research, and its predecessor organizations (the Pediatric Oncology Group or POG, the Children's Cancer Group or CCG, the National Wilms Tumor Study Group, and the Intergroup Rhabdomyosarcoma Study Group), has been at the forefront of collaborative and translational science [9]. The COG's multidisciplinary research team, comprised of more than 7,500 pediatric oncologists, surgeons, radiation therapists, nurses, pathologists, imaging experts, psychologists, pharmacists, cytogeneticists, laboratory scientists, and other allied health professionals at more than 200 leading universities, cancer centers, and children's hospitals, conduct a spectrum of clinical-translational research, with a research portfolio of approximately 100 studies.

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At a national level, however, our cancer clinical trials infrastructure faces a number of challenges. A report from the Institute of Medicine (IOM), “A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program,” details the current problems and suggests pathways forward [10]. An overarching theme of the report, the ability to move new ideas forward towards successful clinical trials in a timely manner, is a primary challenge that faces both the pediatric and medical oncology community alike [11,12]. If we are to successfully capitalize on the era of discovery, we must fully re-evaluate how we develop novel therapeutic approaches for children with cancer, and in doing so, re-invent the approach to our cancer clinical trials system. It is with this goal that the COG has charted its Five Year Blueprint for Research.

For the Children’s Oncology Group’s Five Year Blueprint for Research, scientific leaders from throughout the COG were first tasked to evaluate childhood cancers in the context of the current state of the clinical and biological science. Leveraging this knowledge, leaders were then asked to develop a strategic approach to develop and prioritize the study of targeted new agents in our research portfolio. Similarly, a number of COG’s childhood cancer research disciplines developed strategies that build upon our current knowledge and address critical gaps in our understanding and approach to the treatment of the full spectrum of childhood cancers.

Although our current understanding of the molecular basis for childhood cancers is variable, we can anticipate a rapid increase in this understanding. A primary limitation on therapeutic advance will be availability of agents capable of effectively impacting key targets. Thus, when coupled to our current knowledge of the value of relevant molecular targets, one key set of factors that must be considered in re-aligning our prioritization of clinical trials is the ability, and availability, of targeted new agents. Of equal importance is the current outcome for the cancer sub-populations being considered for clinical investigation. There are clearly a number of childhood tumors that have not benefitted from any meaningful therapeutic advance for many years, and in the absence of a better understanding of their molecular basis, we will likely need to continue rational, but largely empiric, approaches to clinical trials.

Another key challenge will be to design trials that can clearly isolate the effect of the new agent under study. We can no longer afford to conduct large-scale trials that compare regimens that do not afford a clear understanding of the basis for improvement in outcome beyond the comparison of the regimens themselves. Our clinical trial designs must be able to clearly define the effect of therapy that impacts a specific target. Such designs will potentially allow for an extrapolation of results beyond a fixed regimen.

Perhaps the most significant challenge over the next 5 years will be the conduct of phase II trials. Demonstration of significant single agent clinical activity in a relapsed population will continue to be one mechanism to advance a new agent to further investigation. Many new agents, however, will be pursued in the context of combining the novel agent with active but non-curative cytotoxic regimens. While the study of such combinations may provide important feasibility assessments, the potential of such trials to yield reliable efficacy data is inherently limited and potentially fraught with error. As such, pursuit of randomized phase II

trials, including trials that compare distinct targeted agents in conjunction with a common cytotoxic chemotherapeutic regimen, will be but one design approach that merits pursuit.

There is also a need to better position programs to foster enhanced collaboration both nationally and internationally. The ability to develop and execute clinical trials in a timely manner will greatly enhance our ability to partner with biopharmaceutical industry partners. Our already small disease populations will become smaller as the molecular basis for these cancers dissect the historic pathologic classifications of disease into sub-populations potentially requiring distinct targeted therapies. Thus, developing infrastructures that allow for better international collaborative studies is essential. Moreover, exploration of novel designs that can yield interpretable results with smaller populations will be important.

The Children's Oncology Group plans to re-align its resources to take on these challenges. A high level view of the approach needed is shown in Figure 1. Our resources will primarily move to focus on diseases with moderate to poor outcome where our ability to deliver a relevant targeted new agent is high. Conversely, diseases with relatively good to excellent outcomes, with either a limited understanding or ability to administered targeted agents, will not be a near term priority for clinical investigation.

The next 5 years will be both exciting and challenging. Our approach to clinical trials must evolve in concert with the discoveries made in our laboratories. We recognize that as we embark on this 5-year plan, not every aspect of it will be realized. In an era where the pace of discovery is likely to accelerate, COG and other cooperative clinical trial groups need to be positioned to be able to more rapidly respond to advances, and to turn these advances into more effective cures.

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Fig. 1.

The COG plans to re-align its resources to better leverage research opportunities that will emerge during the next era of discovery. For many years, resources have been focused in quadrant IV: diseases for which the outcome is relatively good but the ability or availability of targeted new agents is limited to non-existent. Resources will need to shift towards the shaded region with a focus on quadrant II: diseases for which the outcome is moderate to poor but our ability to deliver a relevant targeted new agent is reasonably high. As we transition resources, there will still be a need to launch clinical investigations for diseases with very poor outcomes despite a limited knowledge of the molecular basis of disease (quadrant I); moreover, strong consideration will be given to diseases with reasonably good outcomes where a highly relevant targeted therapy is developed (quadrant III).