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White Paper on P4 Concepts for Pediatric Imaging

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Abstract

Over the past decade, innovations in the field of pediatric imaging have been largely based on single center and retrospective studies, which provided limited advances for the benefit of pediatric patients. In order to identify opportunities for potential quantum leap progress to the field of Pediatric Imaging, the American College of Radiology - Pediatric Imaging Research (ACR - PIR) Committee has identified high impact research directions related to the P4 Concept of Predictive, Preventive, Personalized, and Participatory Diagnosis and Intervention. Input from 237 members of the Society for Pediatric Radiology was clustered towards ten priority areas, which will be discussed in this article. Needs of each priority area have been analyzed in detail by dedicated ACR-PIR experts in these topics. By facilitating work on these priority areas, we hope to revolutionize the care of children by shifting our efforts from unilateral reaction to clinical symptoms to interactive maintenance of child health.

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Keywords

Pediatric Imaging; Preventive Medicine; Personalized Medicine; Participatory Diagnosis; Image Gently; ALARA

Introduction

The American College of Radiology - Pediatric Imaging Research (ACR-PIR) Committee represents 25 pediatric radiologists who came together to revolutionize the care of children by fostering high-impact imaging innovations with specific emphasis on the P4 Concept of Predictive, Preventive, Personalized, and Participatory Medicine. In 2014, the ACR-PIR committee sent a questionnaire to 350 pediatric imaging experts, who were members of the Society for Pediatric Radiology (SPR), to gather ideas and insights on important areas of development for Pediatric Imaging. Responses of 237 SPR members were clustered towards ten priority areas, which were further ranked and aligned with regards to governmental priorities. In the 2016 NIH appropriations bill, the House of Representatives enacted specific language for funds authorized by the Gabriella Miller Kids First Research Act within the Common Fund, to support the second year of the 10-year Pediatric Research Initiative. Further, to ensure enhanced support for pediatric research, the sponsoring Committee urged the NIH Director to use a portion of the \$10,000,000 made available to the Director's Discretionary Fund (DDF) to support additional pediatric research, such as the development of cutting edge bioinformatics and imaging technologies related to pediatric diseases. This means that the mandatory extra funding of \$12.6M per year for pediatric research (through a separate piece of legislation) will be further supplemented by the NIH Director's discretionary fund by up to another \$10M - and specifically for the priorities listed here. The sponsoring Committee requested quarterly reports on DDF obligations, which shows how important this area has become. The following article will summarize priorities defined by the ACR-PIR committee in this context.

1. Substantially reduce or eliminate radiation exposure of pediatric imaging procedures

Kassa Darge and Christina L. Sammet

To ensure and maximize radiation safety for pediatric patients, ongoing initiatives by the Image Gently Campaign need to be expanded to further major reductions in radiation dose or radiation-free alternatives for imaging studies of children. Several emerging technologies show potential for major reductions in radiation dose while providing equivalent or better diagnostic information compared to existing technologies:

1. *Tomosynthesis*: For many years, advocates of the “*Image Gently*” and “*Image Wisely*” paradigm have encouraged “low-dose” CT protocols. Recently, “tomosynthesis” became available for acquisition of a large number of x-ray projections along an arc, which depict the anatomy of interest from different angles. Tomosynthesis has demonstrated a substantial reduction in radiation compared to

low-dose CT [1, 2]. Early applications in children are promising, including evaluation of the lungs in children with cystic fibrosis [3–5].

2. *Size Specific Dose Estimate (SSDE) and Optimization of Automatic Dose Modulation in Pediatric CT*: The SSDE metric was proposed in 2011 as a way to “child-size” radiation dose in CT [6]. Continued use of the CTDI metric can lead to an underestimation of pediatric radiation dose by a factor of 2–3 and unnecessarily high exposure [6]. Though the validity of the new SSDE metric is well accepted, implementation across a hospital enterprise can be challenging and guidelines for SSDE dose reference levels are limited. Methods for institution-wide integration of SSDE limits have been proposed [7, 8] and need to be further standardized and validated through multi-institutional studies.
3. *Slot-Scan Acquisition in Pediatric General Radiography*: The slot-scan system for scatter reduction is one of the most efficient ways of reducing scattered x-rays, eliminating the need for a grid and reducing radiation dose [9]. Initial results comparing dose in slot-scan radiography to CT are promising, but comparisons with digital radiography are limited. More data are needed to support widespread adoption of this new technology [10–12].
4. *Pediatric Protocols for Interventional Radiology (IR)*: Child-tailored radiation dose protocols in IR, cardiac catheterization labs and other fluoroscopy applications could provide a significant reduction in pediatric radiation exposures. Small changes in the dose per frame and/or pulse rate can lead to major dose reduction [13, 14], but need to be tested against diagnostic yield and clinical impact.

In addition, the ACR-PIR committee identified a opportunities for expansion of radiation-free imaging technologies:

1. *Ultrasound*: [i] **3D/4D US** imaging has widespread use in prenatal imaging and needs to be further extended to new pediatric imaging applications [15–17]. [ii] **US elastography** for assessment of tissue stiffness [18] can be used for grading of liver fibrosis, and needs to be validated in large prospective populations [19–22]. [iii] **Intravenous US contrast agents** improve detection of a variety of pathologies [23, 24], particularly of tumors, inflammatory bowel disease and abdominal trauma [18, 25]. Though the safety of intravenous US contrast agents in children has been established [26, 27]; there is a pressing need to pursue large scale prospective trials on the comparative diagnostic efficacy of unenhanced and contrast enhanced US in children [18, 25]. [iv] **The Oxford Electromagnetic Acoustic Imaging (OxEMA)** system provides MRI-like images, which need to be evaluated for pediatric applications. (www.wadham.ox.ac.uk/news/2014/september).
2. *Advanced MR Imaging Technologies* need to tackle **diagnostic gaps**, such as **MRI of the lungs** [28, 29], multiplexed **MR imaging e.g.** for evaluation of the tumor microenvironment and **MR elastography** for evaluation of organ stiffness [30–33]. The clinical value of positron electron tomography combined with MRI (**PET-MRI**) need to be compared to alternative tests [34, 35].

Impact: The higher risk of radiation exposure in children compared to adults is known. Thus advancing radiation reduction technologies along with implementation of radiation-free alternatives will have significant effect in curtailing the radiation risk in the pediatric population.

2. Improve the safety of pediatric imaging procedures beyond radiation protection

Rajesh Krishnamurthy

There are many other details of imaging procedures beyond radiation exposure which need to be tailored for applications in children: These include investigations of the consequences of a recently recognized deposition of gadolinium chelates in the brain and the effects of sedation on neurocognitive development. Sedation is frequently needed for MRI or CT exams of young children, it leads to fewer diagnostic errors, fewer imaging quality concerns, and fewer incomplete reports [36]. However, procedures vary highly among institutions, based on limited systematic evidence, and long term neurocognitive effects are poorly understood. Although sedation has a highly favorable benefit-risk ratio, it is not without its risks. In 12.5% of procedures, an airway device may be necessary [37]. The risk of hypoxia may be as high as 11% in children sedated with oral chloral hydrate and 17% in children sedated with intravenous pentobarbital [38]. By comparison, Propofol seems to have a more favorable safety profile, with a low rate of 534 respiratory, cardiovascular, and other events per 10,000 anesthetic procedures and no long-lasting morbidity. An increasing concern is the potential risk of neurotoxicity related to general anesthesia, which may lead to impairment of memory later in life [39]. Children who had surgery when they were younger than 3 years had a 60% greater risk of being subsequently diagnosed with developmental disorders than siblings who did not undergo surgery [40]. Owing to this increasing concern, necessary steps to improve the safety of imaging procedures in children are:

1. Collecting multi-institutional evidence and generating expert guidelines for use of medications with potential for immediate or long term neurotoxicity
2. Developing creative alternatives to eliminate the need of potentially harmful medications for imaging studies of small children
3. Develop decision algorithms for patient stratifications to imaging studies with ALARA risks (as low as reasonably achievable)

Impact: Revisiting, refining and unifying the safety of imaging techniques for children will substantially impact our goal of preventing unwanted long term adverse effects.

3. Develop imaging registries for collection of “big data”

Andrea S. Doria and Ellen Chung

The increasing global connection between health care providers and families worldwide provides huge potential for improving the health of children beyond high end academic centers. There are 4.6 billion mobile-phone subscriptions worldwide and there are between 1 – 2 billion people accessing the internet every day [41]. Imaging data obtained at pediatric

hospitals worldwide should be collected in shared image registries to obtain normative data about the growing child, eliminate repeated or comparative imaging studies, standardize imaging strategies and establish reporting guidelines across institutions. These image registries could serve as a resource for both patients and physicians. The collected information from large populations could allow experts at academic centers to develop new solutions for key clinical questions regarding normal child development, better diagnoses, improved therapy outcomes and patient-perceived value [42–44]. Towards this end, the following roadmap could help generating pediatric imaging registries:

1. **Unify and standardize information:** Multidisciplinary consensus should be obtained on terminology, protocols, metrics, and radiation safety (if applicable) for integrative clinical and imaging data registries. A global image registry could enable review of normal findings in children according to age, gender and ethnicity, among others.
2. **Enable flexible access to multi-dimensional information:** It should be easily possible to select data according to genomic, anatomic, disease-related or functional (CT, MR, US etc.) categories, among others. Clinical and laboratory (serum/urine) biomarkers should be included whenever possible.
3. **Enable Networking:** Diagnostic databases could serve as a platform for partnership and networking, which could enhance professional knowledge and foster decision support. The collected data could be used to establish widely accepted standards and guidelines for specific pediatric disorders.
4. **Monitor Regulatory Compliance:** Creative solutions and regulatory oversight will be needed to ensure access to and confidentiality of patient data in trans-institutional registries.

Impact: Pediatric image registries could help to establish global resources and standards for imaging protocols and quantitative metrics for normal child development, which could facilitate more accurate diagnoses worldwide.

4. Develop disease-specific imaging biomarkers

Stefan Voss

Imaging has a unique opportunity to improve treatment decisions and successful treatment outcomes through identification and validation of new biomarkers. The Biomarkers Consortium was launched in 2006 with the goal of identifying new biomarkers that have the potential to enhance the detection, diagnosis, and treatment of pediatric diseases. For example, for patients with cancer, there is an urgent need to validate and improve existing and new imaging biomarkers through multi-institutional initiatives and develop agents with improved diagnostic accuracy, such as ^{18}F -MFBG. Incorporation into hybrid imaging techniques (PET/MR) will foster time- and cost efficiency through “one-stop diagnoses”. Other examples of imaging biomarkers for the pediatric population include biomarkers for neurocognitive function, bone health and obesity, among many others. Childhood obesity has emerged as a major health concern, affecting 30–77% of overweight children in the United States and leading to nonalcoholic steato-hepatitis, insulin resistance, liver cirrhosis

and end-stage liver disease. MRI with proton MR spectroscopy of the liver, opposed-phase MR imaging, MR elastography and sonoelastography have gained recent attention as measures of liver steatosis and cirrhosis and need to be further validated in large patient populations. Important pathways to the development of novel pediatric imaging biomarkers are:

1. Identify clinically relevant questions and unmet needs specific to the growing child. Evaluate existing and new biomarkers for relevant pediatric applications in proof-of-concept studies.
2. Validate biomarker through large-scale prospective, randomized clinical trials
3. Integrate information from multiple biomarkers, determine the most time- and cost-efficient combination
4. Link imaging biomarkers with clinical outcomes: predictive, prognostic and diagnostic information, therapy response and disease recurrence

Impact and Challenges: Integrating our understanding of the molecular basis of disease will foster the development of predictive biomarkers and enable personalized treatment approaches. Advanced imaging biomarkers could help to prevent clinically symptomatic disease, provide more accurate diagnoses and guide personalized therapies.

5. Advance quantitative image analyses and computational methods for radio(gen)omics

Andrew Trout, Ashok Panigrahy, Alex Towbin

There is a growing recognition that imaging data contain hidden information (sometimes in plain sight). For example, in oncology, tumor aggressiveness, treatment approach and outcomes are not any more determined any more by tumor location, but by genomic profiles. Linking this information to specific characteristics on imaging studies requires fundamental advancements in how we analyze medical images. To this end, advances in bioinformatics will be critical to improve the clinical yield of imaging tests by extracting complex information through data mining and artificial intelligence, and providing computer-assisted recommendations for personalized therapies. Quantitative imaging data and radiogenomic data associations, suggested based on small-scale, single center studies [45–51] need to be validated in large-scale clinical trials through cross-institutional collaborations. Technological advances will likely expose us to full genome data of every patient in the near future, which need to be analyzed within the larger framework of family exome and genome sequences to identify multigenetic traits. In addition, microbiome data can be integrated within complex data bases, with special consideration of geographical or cultural contexts and in order to prescribe personalized diagnostic imaging tests and interventions. Important steps towards successful links between biological codes and imaging include:

1. Generate large-scale trans-disciplinary data bases of Genomics, Proteomics, Microbiomics, Metabolomics, Epigenetics and Clinical Imaging Data
2. Develop, validate and integrate new quantitative imaging biomarkers for novel biological targets

3. Develop means to efficiently and effectively connect imaging data and biological code information through intelligent data mining approaches

Impact: Integrating quantitative image analyses and radio(gen)omics will impact the current practice of medicine by (1) predicting disease before it becomes clinically symptomatic, (2) prescribing personalized therapies; (3) improving personalized treatment response monitoring; and (4) individualizing point-of-care therapy.

6. Develop transformative interventions

Matthew Lungren, Anne Marie Cahill

Despite decades of success for adult patients, children have largely remained underexposed to advanced interventional procedures. Minimally invasive image-guided interventions, such as transarterial embolization, ablative techniques, and, in the future, gene therapy, are increasingly being used in the management of a variety of diseases, particularly malignant tumors.[52] [53] Transcatheter arterial chemoembolization (TACE) has shown promising results in patients with malignant liver tumors [54–57]. Hundreds of studies in adults demonstrated that TACE can efficiently shrink tumors before surgery or selectively treat inoperable tumors with fewer side effects compared to systemic therapy. However, therapy protocols associated with large cooperative clinical groups such as the Children’s Oncology Group and the International Society of Pediatric Oncology rarely include interventional radiology options. Promising interventional radiology techniques for pediatric patients include radiofrequency, microwave, and cryoablation [58]. In addition, high-intensity focused ultrasound (HIFU) has been successfully applied to non-invasively ablate benign and metastatic bone tumors and other malignancies [59]. HIFU is non-invasive and ionizing radiation-free, and an extracorporeal MR-guided HIFU device has been approved by the Food and Drug Administration (FDA) for clinical treatment of bone metastases. Other new interventional oncology therapies on the horizon include selective arterial delivery of gene therapies combined with vessel embolization to limit adverse effects and prolong agent dwell time [60, 61]. A strengthened bidirectional feedback loop between interventional radiologists and oncologists would enable us to continuously inform clinicians about new discoveries and capabilities on either side. The following steps would support clinical translation of interventional innovations for the benefit of pediatric patients:

1. Coordinate Pediatric IR efforts nationally and internationally through existing or new disease-focused consortia
2. Create interactive platforms for collection of creative approaches to clinical problems specific to pediatric patients and unite investigators at different institutions to test the most promising approaches in large scale multicenter prospective clinical trials
3. Initiate procedure registries which provide information about clinical outcomes of personalized interventional procedures in children
4. **Impact:** Novel strategies will enable pediatric interventional radiology practitioners to provide cutting edge minimally invasive image-guided treatments as an adjunct or alternative to surgery for pediatric patients.

7. Nanomedicine for Pediatric Molecular Imaging Applications

Heike E. Daldrup-Link

Integrating nanomedicine with novel multi-modality imaging technologies spurs the development of new personalized diagnostic tests and theranostic (combined diagnostic and therapeutic) procedures.

Iron Oxide Nanoparticles as Contrast Agents—Ultras-small superparamagnetic iron oxide nanoparticles (USPIO), such as ferumoxtran-10 (Sinerem or Combidex) and ferumoxytol (Feraheme™) can be used as contrast agents for MRI [62–67]: Ferumoxytol is FDA-approved for treatment of anemia in adults and can be used “off label” for MR angiography and tissue perfusion studies [67]. After an initial distribution in the blood pool, ferumoxytol nanoparticles are slowly phagocytosed by macrophages, which can be used for tumor detection in liver, lymph nodes and bone marrow, [63] or diagnosis of inflammatory processes [68]. In addition, iron oxide nanoparticles like ferumoxytol can be applied for *in vivo* tracking of stem cell transplants [62]. Since ferumoxytol is not associated with risk of nephrogenic sclerosis, it can represent an alternative to gadolinium chelates in patients with renal insufficiency or if creatinine values are not available [63, 64]. However, ferumoxytol can rarely lead to severe anaphylactic reactions. Given unique imaging applications, further investigations of the safety of nano-materials specifically for pediatric patients are urgently needed.

Nanoparticles as Theranostic Agents—Nanoparticles can be more selectively delivered to tumors than conventional contrast agents [69]. Therefore, nanoparticles can be linked to therapeutic drugs and utilized for combined diagnosis and therapy of cancers [70] and image-guided drug delivery. [71–73] The NCI Experimental Therapeutics (NEXT) program is a great resource for development of novel nano-theranostics.

Nanoparticles as Screening Agents—Novel developments are under way of orally administered nanoparticle compounds, which are absorbed through the gastro-intestinal system, enter the blood pool, bind to specific cancer-related molecules in a bloodstream, and could be detected by wearable devices. [74–77] Needle-less deliver of these new biomolecules is particularly appealing for pediatric patients and needs to be validated against traditional diagnostic approaches. Pathways towards translating novel nanoparticles to clinical practice are:

1. Develop child-tailored nanoprobe, e.g. through co-clinical trials (<http://www.wmis.org/wmis-to-collaborate-with-nci-on-expansion-of-co-clinical-trials/>), orphan drug designations, or the NCI MATCH program (<http://www.cancer.gov/researchandfunding/areas/clinical-trials/nctn/match>)
2. Evaluate the safety of novel nanoparticle compounds with attention to specific safety concerns in pediatric patients, e.g. long term impact of imaging probes on neurocognitive development
3. Prove the value of novel nanoparticle compounds for patient management and outcomes

Impact: New child-adapted nano-technologies can be expected to substantially improve our knowledge of pediatric health and disease, thereby fundamentally changing the way we practice medicine, from detecting and treating disease to maintaining human health.

8. Develop novel data processing tools, such as 3D printing and bioprinting

Laura Olivieri and Katherine Barsness

3D printing is an evolving technology, which is being integrated into the management of congenital malformations, genetic anomalies, and human structural disease. The key to successfully treating these conditions, which affect children disproportionately, is to understand their patient-specific severity and extent. For example, congenital heart disease occurs along a spectrum of severity, which may require completely different surgical approaches. The same is true for airway, gastrointestinal, gynecologic, and urologic malformations. There is a growing body of evidence demonstrating clinical utility of 3D models in structural human disease [78–81]. Due to the relative rarity of these defects, multi-center assessments are needed to evaluate the clinical impact of 3D printing technologies on clinical outcomes. Outcome measures might have to be defined based on procedural efficiency and educational utility rather than simple “repair” of a structural defect. The expense of adding 3D printing technology to clinical or educational pathways must be examined against savings of surgery and anesthesia time through better prepared surgeons [82]. To realize the full potential of 3D printing for pediatric malformations and diseases, there are a number of challenges that will need to be addressed:

1. Develop dedicated image segmentation technology to provide point-of-care processing and creation of patient-specific models. Develop post-processing technology to display and annotate both digital and printed 3D models in order to streamline the process
2. Establish workflows for clinical integration of novel 3D printing and bioprinting technologies.
3. Initiate multi-center trials to define the clinical impact of 3D models.

Impact: 3D printing technologies have the potential to revolutionize our understanding of human malformations, change the way surgeons and interventional practitioners approach and plan procedures to correct these malformations, and give us the ability to create custom, patient-specific, implantable prostheses.

9. Reduce Costs for Pediatric Imaging Procedures

Sheila Moore

The United States’ health care spending far outpaces that of other industrialized countries, spending approximately \$9000 per capita on medical care (*Davis, KL; Hospital Mergers Can Lower Costs and Improve Medical Care; WSJ 9/15/14*). In addition, American medicine is transitioning to a population health care management model, in response to multiple forces including the Affordable Care Act, and the needs to reduce health care costs while facilitating quality care. Creative approaches are needed for substantially reducing health

care costs without impairment in quality of care. Examples of potential questions under this effort include evaluations of first time seizure patients with brain MRI, often under sedation. Approximately 2–5 % of Americans experience an afebrile seizure, with 71% being 15 years or younger. [83] We need to evaluate how many of those studies have actionable findings to calculate a cost benefit ratio for imaging first time seizures in children. Another important focus for multi-institutional research efforts is the cost benefit ratio of urine pregnancy tests in girls over 10 years of age before imaging. Important steps towards cost reduction in clinical imaging are:

1. Eliminate low yield imaging tests and unnecessary procedures.
2. Work closely with different fields to establish escalating diagnostic procedures: Screen with less expensive laboratory tests, escalate to low and high cost imaging for selected patients. Accelerate advanced imaging procedures to reduce costs.
3. Identify areas where imaging can help save costs on expensive therapies (e.g. monitoring cancer therapies). Develop intelligent diagnostic-therapeutic algorithms to minimize or eliminate patient exposure to inefficient therapies.
4. Improve workflows such that despite escalating diagnostic steps, all of these can be performed in one visit.

Impact: Radiologists should support time- and cost-efficient health care for children by prescribing “the right test at the right time,” eliminating unnecessary procedures, and promoting personalized, safe, high quality imaging tests.

10. Develop wearable diagnostic devices and “at home” imaging tests

The development and exploration of wearable diagnostic devices and “at home” imaging tests are in a nascent stage but have significant potential for revolutionizing health care from sporadic physician-driven diagnoses of clinical symptoms to continuous self-monitoring of human health and subclinical disease. Our patients and their parents want to be involved in evaluations of their health status and they embrace developments of self-measuring devices [74–77]. A variety of new mobile diagnostic technologies are currently under development, which can be applied by the patient or family/caregiver at their home, and transferred to a physician and radiologist for remote interpretation. These new patient-driven health-monitoring devices have great potential as screening tools and need to be validated against and integrated with traditional diagnostic approaches. Examples include wearable surveillance monitors for patients with chronic diseases, personalized genomics services [74], wireless, non-invasive glucose and other blood biomarker measuring devices [77], wireless blood pressure, EEG and electrocardiographic sensors in removable body patches, and pressure sensors in textiles for people with paraplegia [75], among many others.

In summary, the ACR-PIR initiative is dedicated to foster high-impact diagnostic and therapeutic imaging innovations through multi-institutional trans-disciplinary research in order to enable quantum-leap advances for the benefit of our pediatric patients. The described research priorities should help to shift our focus from unilateral diagnosis of clinical symptoms to interactive maintenance of child health.

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Conflict of Interest:

Heike E. Daldrup-Link, MD, PhD:

Dr. Daldrup-Link reports grants from NIH, during the conduct of the study; In addition, Dr. Daldrup-Link has a patent 13/923,962 licensed to Stanford University, a patent 14/161,315 licensed to Stanford University, and a patent UK 13-005 licensed to University of Bradford, UK and Stanford University.

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Take-Home Points

- Multi-Center prospective research initiatives are needed to enable quantum leap advances in the field of Pediatric Imaging.
- The P4 concept of Predictive, Preventive, Personalized, and Participatory Medicine needs to be tailored for specific needs of pediatric patients.
- Image gently initiatives need to be expanded towards imaging tests that avoid sedation and imaging tests that avoid long-term biomarker retention
- Establishing child-focused trans-disciplinary image registries and cutting edge bioinformatics tools will enable integration of biological code information with advanced imaging tests
- Alignment of ACR-PIR priorities with existing and evolving governmental research investments will catalize innovative ideas and initiatives.

Summary Sentence

ACR-PIR initiative is dedicated to foster high-impact diagnostic and therapeutic imaging innovations through multi-institutional trans-disciplinary research in order to enable quantum-leap advances for the benefit of our pediatric patients.

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