Implementation of PPI Medication PGX Testing

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Nemours.

RESEARCH PLAN

I. **SPECIFIC AIMS** *(Not to exceed 1 page)*

The potential for incorporating genomic information into a patient's clinical care for the purpose of improving drug therapy; i.e., personalized medicine (or precision medicine), has been anxiously anticipated since the publication of the Human Genome Project and the Hap Map project. The FDA has approved a list of pharmacogenomic tests, which can be ordered to guide drug treatment. However, clinical implementation of pharmacogenomic (PGX) testing has been disappointing owing to challenges and barriers related to analytical uncertainties, misunderstanding of genetic testing among stakeholders and cost. Recently President Obama announced the Precision Medicine Initiative, which include PGX testing, and has earmarked $ 1 B to implement it. The Precision Medicine Initiative is expected to move personalized medicine forward so that all patients including children will benefit. The Nemours Children's Health System is uniquely position to lead the effort to personalize medicine among pediatric patients. This proposal seeks to implement a pilot, proof-of-concept PGX implementation study in the GI clinic at Nemours Children's Hospital in Orlando, and proposes to begin with PGX testing of the CYP2C19-proton pump inhibitor gene-drug pair. Proton pump inhibitors (PPI) are one of the most highly prescribed drugs in the world; are extensively used in pediatrics to treat gastroesophageal reflux (GER) and other related conditions; and are thought to be safe. All PPI are substrate for CYP2C19, which is expressed in the liver and encoded by the CYP2C19 gene. Loss- and gain-of-function SNPs yield poor and extensive metabolizer phenotypes respectively, which result in plasma levels that can vary 10-fold depending on metabolizer phenotype following the administration of similar PPI doses. Thus, the dosing of PPI to treat GER according to FDA-approved guidelines often results in under treatment and poor therapeutic response in extensive metabolizers and to toxicity in poor metabolizers. We have submitted an R01 application titled: Pharmacogenetic Approach to Optimizing Proton Pump Inhibitor Treatment in Children, which is in response to: PAR 14-274 Pharmacogenetics, Pharmacoepigenetics and Personalized Medicine in Children (October 5, 2014 deadline). The PAR recommends that applications include a clinical trial in which we proposed to compare conventional and genotype-guided dosing of PPI in children with GERD. If funded, we will return the unused portion of this application to Nemours Research; if not funded, we will resubmit our R01 application using preliminary data gathered from the present project. The primary goal of the present project is to test the feasibility of a simple, point-of-care PGX testing* service in Nemours Children's Hospital.

*Point-of-care testing (POCT) is defined as medical testing at or near the patient's bedside, and can be accomplished using labor that requires no specialized or professional training. Although the device we propose to use (SPARTAN RX) is a POCT device it will be housed in the Division of Pathology at Nemours Children's Hospital and not at the bedside or the GI clinical. Therefore, what we propose is technically not POCT.

Aim 1: To implement pharmacogenomic (PGX) testing at the Nemours Health System

1a: To determine the feasibility of point-of-care PGX testing the CYP2C19-PPI gene drug pair in children with GERD or other stomach acid mediated conditions for which a PPI is prescribed at Nemours Health Systems, Nemours Children's Hospital, Orlando.

1b: Evaluate the safety and efficacy of genotype-guided dosing of PPI in children.

II. **BACKGROUND AND SIGNIFICANCE** *(Not to exceed 3 pages)*

Clinical implementation of PGX testing has been disappointing owing to several barriers, which deny patients the benefits of safe and effective drug therapy. In this section we discuss those barriers and demonstrate how

the Nemours Health System is uniquely poised to implement PGX testing. This will benefit Nemours patients and their families and will provide a model for other health systems, hospital and primary sites to emulate. The rationale for selecting the CYP2C19-PPI gene-drug pair is discussed in this section.

II.1 Barriers to PGX implementation. The incorporation of genetic information into the individual patient's medical record for the purpose of guiding drug treatment in this country is slow owing to challenges and barriers including some that are unique to the pediatric population (1-4). The implementation of PGX testing at NHS will benefit Nemours patients and their families by improving efficacy and reducing the risk of adverse events related to drug treatment. Successful implementation of PGX testing at NHS can serve as a model for other pediatric health systems, hospitals and primary sites to follow thus accelerating the rate of PGX implementation in this country.

The absence of clear guidelines that facilitate timely implementation of PGX into the clinic is a barrier that drove the establishment of Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2009, by the Pharmacogenomic Research Network. One of the goals of CPIC is to provide evidence-based guidelines for gene-drug pairs that could be used to improve drug treatment 2. The CPIC has established a framework for applying the types and levels of evidence required to justify incorporating genetic information into a patient's medical records to improve drug efficacy and/or reduce toxicity 2. The quality of the evidence linking genetic variation and drug effects can be stratified into 3 levels (and recommendations): level 1: consistent evidence from well designed studies (strongly recommended); level 2: sufficient evidence that is limited by number, quality and consistency of studies, or by the inability to generalize to clinical practice (moderate recommendation); level 3: insufficient evidence (optional recommendation)2.

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II.2. Rationale for testing the CYP2C19-PPI gene pair for PGX implementation.

II.2.1. PPIs are used extensively for approved and unapproved conditions in pediatrics. Proton pump inhibitors (PPIs) are the most potent and effective class of gastric acid suppressing drugs (5-8) and are among the highest selling prescription (not including over-the-counter sales) drugs in the world (9-11). More than 75% of patients receiving long-term PPI treatment have no approved indications for use (12). PPI are used in neonates and pre-term infants for unapproved conditions including gastric acidity, problems feeding, esophagitis and gastric pain (13-16); asthma (17,18) and for food allergies (19-21). This is of particular concern to the FDA (22) because of questions of PPI efficacy and safety in children (23-25), and are not recommended without evidence of acid-induced disease (22,26). Dosages of PPI for unapproved use are based on the dose recommendations for GERD.

II.2.2. PPI use is associated with gastric and respiratory infections. Chronic use of PPIs has been associated with unexpected side effects including gastric and respiratory infections, which are thought to be related to the gastric acid suppressive properties of PPIs (27,28). The acidic pH of the gastrointestinal tract represents a protective barrier from invasion by ingested pathogens (29,30). Chronic gastric acid suppression by PPIs (and H2antagonists) reduces the effectiveness of this protective barrier and increases the risk of bacterial colonization in the upper gastrointestinal tract (29-33) (reviewed in:34-40). Of critical importance, the adverse effects associated with PPI use are dose-dependent. For example, the risks of nosocomcial C difficile infection was proportional to the intensity of suppression (no suppressive treatment; H2 antagonists, daily PPI and twice or more PPI administration/day) among patients receiving gastric acid suppression C difficile infection 32 (see Figure 1; in appendix). If aspirated during reflux episodes infected gastric media increases the risk of upper respiratory infections (41,42). Several studies have reported that the chronic use of PPIs has been associated with community-acquired pneumonia in children and adults (34,43-49). In a study of lansoprazole in infants, lower respiratory tract infections occurred more frequently in participants on drug compared to placebo (25). In a recent study of lansoprazole in children with asthma (ACRC study; PI is an author), the prevalence respiratory infection was higher among those getting the PPI compared to placebo (17).

II.2.3. Pharmacodynamics and pharmacokinetics of PPI are dependent on CYP2C19 haplotype. The efficacy of PPIs is strongly correlated with plasma concentrations (50,51). The pharmacokinetics and pharmacodynamics of most PPIs are influenced by CYP2C19 polymorphisms (reviewed in 52-55). Several loss-of-function alleles reduce drug clearance and increase plasma concentrations of PPI resulting in individuals being classified as either poor metabolizer (PM) or intermediate metabolizers. CYP2C19*1 alleles are wild type (WT), and are associated with a more rapid clearance and lower concentrations of PPI, which results in individuals being classified as extensive metabolizers (EM) (56) (http://www.healthanddna.com/2C19tech.pdf). CYP2C19*17 is a gain-of-function allele that increases the clearance of PPIs and decreases drug concentrations even below those observed in individuals classified as extensive metabolizers. Individuals carrying *1/*17 alleles contribute to the ultra rapid metabolizer (UM) phenotype (57,58). Individuals with GERD who carry 2 CYP2C19*17 alleles (homozygous ultra rapid metabolizers) require higher doses of PPI to obtain optimal acid suppression (52,53) (see Table 1 in Appendix). The area under the plasma concentration vs. time curve (AUC) for omeprazole and lansoprazole (and other PPIs) is 3- to 10-fold higher among poor metabolizers PMs compared to extensive metabolizers EMs given equal doses (54,55,59,60). While more studies are needed in children, CYP2C19 variation appears to influence PPI pharmacokinetics in children (58,61,62).

II.2.4. Link between PGX and PPI efficacy and adverse events. The link between PPI efficacy and PGX is well established: cure rates for H pylori were significantly higher in PMs compared to EM (52,63). Additionally, high doses of PPI have been used to successfully treat EMs with H pylori (52,59). Thus the quality of the evidence linking PPI efficacy in GERD and related conditions to CYP2C19 variation is level 1 and PGX testing has been recommended to avoid treatment failures (55). In constrast the evidence linking PGX with PPI-associated adverse events is one authored by the PI of this submission (64). The applicant compared the prevalence of respiratory infections in poor metabolizers (carriers of CYP2C19*2, *3, *8, *9; N=45) with extensive metabolizers (carriers of 2 WT CYP2C19*1 alleles; N= 91). The OR for upper respiratory infections (URI) was higher in PM compared to placebo: 2.46 ($p<0.05$) but not in EM compared to placebo: OR = 1.55 ($p=0.15$) (See Figure 2 in appendix). Mean ± SD plasma concentrations of lansoprazole were 57% higher in PM compared to EM, thus supporting reduced clearance of and greater exposure to lansoprazole in EM compared to PM. (see Figure 3 in appendix). Clearly, the evidence linking CYP2C19 variation and PPI-associated respiratory infection is level 3 owing to the fact that ours is the only published study to demonstrate a link between CYP2C19 variation and PPI toxicity. Notwithstanding the level evidence, we recommend PGX testing for the CYP2C19-PPI gene pair not only based on our work but also because of the following: (i) the body of knowledge about the link between PPI-induced acid suppression and dysbiosis and the association between PPI use and respiratory and gastric infections is unequivocal; (ii) the proportional relationship between PPI dose and C difficile infection and between PPI dose and the prevalence of community-acquired pneumonia is unequivocal. Failure to adjust the dose of PPI in poor metabolizer children will unnecessarily expose them to increased risk of infection. Implementing PGX testing for the CYP2C19-PPI gene pair at the Nemours Children's Hospital will allow us to personalize PPI dosing based on CYP2C19 genotype, which will reduce the risk of infection.

III. **PRELIMINARY STUDIES/PROGRESS REPORT** *(Not to exceed 3 pages)*

Preliminary Data. Conventional doses of PPI can result in inferior response in EMs and a therapeutic response in PM. Some children undergo esophagogastroduodenoscopy (EGD) and biopsy if they fail to respond to PPIs. It is possible that CYP2C19 genetic variation may contribute to poor response to PPI. We hypothesized that the frequency of EM phenotype would differ in EGD patients compared to controls. First, we genotyped biopsy samples in 29 individuals for the *2, *3, *8, *9 and *17 SNPs and compared them to saliva collected from the same individuals to establish congruency between the two samples. 28/29 genotypes were congruent; one sample of tissue did not produce a signal. Next we compared the frequencies of genotypes among biopsied samples who were either on or had been on PPI (N=18) and controls (90 adult asthma patients) and the results are shown in Figure 2 in appendix. The frequencies of *17 alleles did not differ (0.17 vs. 0.15) but the frequency of *2 allele was significantly lower in EGD children (shaded bars) vs. control (un-shaded bars): 0.028 vs. 0.19 p =0.04. These data are consistent with PMs having a better acid suppressive

response to PPI than other phenotypes and suggests that NMs and EMs who are prescribed EGD may be under-dosed with PPI. These data are important to the project because they show that CYP2C19 genetic variation influences response to PPI. In addition to tissue we have analyzed (Figure 2), we have received tissue from Nemours in JAX, ORL and in Wilmington for children who were on PPI and were tested in 4 distinct cohorts: GERD + pH probe; Cystic Fibrosis; Fundoplication; Inflammatory bowel disease (IBD) + Cdifficile. We plan to obtain 100 samples from each cohort to explore our hypothesis in these children.

IV. **RESEARCH DESIGN AND METHODS INCLUDING STATISTICAL ANALYSIS** *(Not to exceed 10 pages)*

The Nemours Children's Health System is uniquely positioned to implement PGX testing in pediatrics. We propose to initiate this pilot study at Nemours Children's Hospital in Orlando. Long-standing and award-winning entities operating under the Nemours Health Informatics that continuously evaluates and updates CDS tools, professional educational tools and patient-family education tools is innovative. These programs will eliminate several of the barriers to PGX implementation including uncertainties about which test to order, how to act on this genetic information and the uncertainty among patients and their families about genetic testing. They will also rapidly and efficiently make changes as the need arises. Some of these programs (listed below) will be utilized in the proposed pilot study.

IV.1. Nemours Health Informatics: Nemours was among the first institutions to use an electronic health record (EHR) (Epic Systems, Verona, WI) in a multispecialty pediatric group practice beginning in 1998 with rollout to all Nemours campuses completed by 2005. Because Nemours has been an early adopter of electronic health record implementation and has received awards for excellence in healthcare information, the institution is poised to embrace expansion of pharmacogenomic efforts.

IV.2.Medication List Review for Every Inpatient and Outpatient Encounter. The initiation of virtually all patient encounters includes the review of active medications with the patient/family and Nemours exceeds the national standard for medication reconciliation. At each visit, digitally created prescriptions (when e prescribing is not used) and supportive consumer content are provided at every visit. Prescription pads are not permitted. The accuracy of our medication lists has increased significantly as a result, and therefore the accuracy of clinical decision support has also increased.

IV.3. Laboratory Testing: Lab results from external lab sources are digitally interfaced with the medical record using the SunQuest Laboratory Information System (http://www.sunquestinfo.com/products-solutions/laboratory/ laboratory/). Test results will be integrated into NemoursOne (EPIC) template that provides interpretation and recommendations for dosing or alternative treatments.

IV.4. Clinical Decision Support (CDS) Usage and Outcomes in Place at Nemours;. For over five years, each of the Nemours site-specific-physician specialties have identified one or more clinical quality process measures that if enhanced, could result in improved outcomes and quality of life. The corresponding metrics are gathered via NemoursOne and results are benchmarked against national standards. Furthering alignment with strategy, every clinician has 5% of salary "at risk" for their measured patient outcomes. An assortment of CDS tools are available to clinicians including; "Smart" tools provided by Epic (templates, forms, lists, phrases); a highly customized Epic configuration; library and web resources within the Epic desktop; custom (home grown) applications and applets; and commercial CDS solutions. Thus, Nemours has the infrastructure in place to develop the CDS tools to be used for PMT and CYP2C19 testing.

IV.5. QlikView for Outcomes Analysis. QlikView is a business discovery tool at Nemours (http://home.nemours.net/clinical/ehr/mynemours.html) that integrates data from any source including the Nemours Data Warehouse, NemoursOne, external sources, and office programs. The Nemours Data Warehouse is a mission-critical facility that houses extracted data from NemoursOne, secondary Clinical Systems, expense cycle systems and other applications for reporting in support of: clinical analysis, research

studies, revenue and expense analysis, compliance reporting, performance metrics, risk management and infection control, market analysis, patient satisfaction, reporting to external agencies and entities, and other ad-hoc areas. With QlikView, clinicians, administrators, researchers and others can access de-identified aggregate data on demand.

IV.6. Nemours University: Nemours University provides online computer based curriculum to all Nemours staff and has been the recipient of numerous awards including the American Society for Training and Development BEST award and the Leaning! 100 Award. Nemours University will be used to develop online training programs for clinicians who will be ordering pharmacogenomic tests for CYP2C19 testing. Curricula can be included as part of required training and will include general training on genetics as well as training on the PGX section that will be newly added to NemoursOne.

IV.7. KidsHealth: KidsHealth at Nemours creates engaging, family-friendly online, video, and print media for parents, kids, and teens. KidsHealth's flagship project, http://kidshealth.org/, is the largest provider of online and video content about children's health and development in the world, and is a resource for families, educators, physicians, and the media. It is the #1, most-visited site devoted to children's health in English and Spanish and on a typical weekday, KidsHealth gets more than 1 million visits per day. KidsHealth is winner of numerous awards. KidsHealth modules also include audio links to have the modules spoken aloud for those viewer who have low literacy.

IV.9. MyNemours: MyNemours (https://mynemours.nemours.org/) is a free, confidential, internet-based tool that gives parents and legal guardians secure electronic access to select portions of their child's medical records and health history at home. In this proposal, MyNemours will serve several functions: to obtain electronic informed consent for genetic testing per the requirements of state laws as well as for storage and future use of genomic materials and data, to desseminate explanations of individual genomic testing results, and to query patient satisfaction with PGX information provided.

IV.10. Ensuring Consistent Clinical Care Across Nemours Campuses.

Nemours Clinical Management Program (NCMP) is an enterprise-wide initiative that focuses on reducing unwanted variability in clinical care. To achieve this, NCMP uses principles of evidence-based medicine to establish Nemours Standards of Care, creates tools to measure adherence to these standards, and analyzes the outcomes of care. By analyzing meta-tagged clinical data elements, NCMP can measure and model clinical outcomes and thus allow quality assessment teams to prospectively monitor care metrics and institute quality improvement initiatives..

IV.11. Nemours Office of Human Subjects Protection (NOHSP) and Nemours Institutional Review Board (IRB): The Nemours Office of Human Subjects Protection (NOHSP) has oversight of institutional policy and procedure regarding human subjects protection, including operational oversight of Nemours' Institutional Review Boards.

In summary, the informatics infrastructure that Nemours has in place is well established and highly functional, and provides an optimum environment for expanding PGX services in the future. This pilot project will enable us to efficiently incorporte Nemours IT as we move forward with PGX testing at Nemours.

Specific aim 1a: To determine the feasibility of point-of-care PGX testing the CYP2C19-PPI gene drug pair in children with GERD or another clinical condition for which a PPI is prescribed at Nemours Health Systems, Nemours Children's Hospital, Orlando.

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Study design: Our study is an 'open label' design in which potential participants will be recruited by GI staff of NCH in Orlando. All potential participants will be children, 2 to 17 yo, presenting with symptoms of GERD or other stomach acid mediated conditions for which a PPI is prescribed . The pediatric gastroenterologist will prescribe PPI of his/her choice (PPIs used at Nemours include lansoprazole, omeprazole, esomerazole and pantoprazol). If patients/caregivers agree to participate, they will be asked to read and sign the informed consent/assent documents and undergo screening to determine if they meet the inclusion criteria (see below). Participants will volunteer to submit a saliva sample for the determination of CYP2C19 genotype and metabolizer phenotype.

Genotyping. Genotyping will be performed using Spartan RX. Figure 5 in appendix depicts the device along with a sample print out showing the haplotypes and metabolizer phenotypes for *2, *3 and *17 alleles.

Experimental Plan. The specific events between a diagnosis of GERD or other stomach acid mediated conditions for which a PPI is prescribed and the prescription for the PPI are summarized as follows:

1. Diagnosis of GERD or other stomach acid mediated conditions for which a PPI is prescribed will be performed by a pediatric gastroenterologist at the Nemours Children's Hospital. Dr. Franciosi will explain the experimental pilot study and plan to his Division; he has has committed to participating in this pilot project. Other GI pediatricians will be invited to participate (participation is not required).
2. After the diagnosis of GERD or other stomach acid mediated conditions for which a PPI is prescribed and decision to use a PPI are made, consent will be obtained from patient and family and the PGX test will be ordered (Molecular Diagnostic Lab). Consent will also be sought for storing saliva for future PGX testing. Patients are not required to provide a saliva sample or to agree to genotype-guided dosing of PPI.
3. Saliva sample will be collected; bar-coded; and analyzed by SPARTAN RX point-of-care system housed in Department of Pathology, NCH (CLIA-accredited). Genotype results are available <60 minutes.
4. Test results will be integrated into NemoursOne (EPIC); Clinical decision support (CDS) tools will provide interpretation and recommendations for PPI dosing or alternative drug and an E prescription will be ordered. Tables for conventional and genotype guided dosing are shown in Tables 2 and 3 of appendix.

Outcome Metrics. Outcomes for evaluating the success of PGX implementation include the following:

% of patients agreeing to volunteer for the study

% of patients reporting efficacy and toxicity data

% of providers agreeing to participate in study

% of participants agreeing to future use of DNA

Sub aim 1b: Compare safety and efficacy of genotype-guided for PPI.

Outcome metrics for response to PPI.

The primary outcome to assess the efficacy of PPI therapy will be scores calculated from a validated questionnaire specifically designed for children with GERD (65) (see Figure 6 in appendix). The PI and his team have experience using this tool (17). Briefly, participants and/or parents and guardians will assess frequency and severity of the following symptoms in the preceding 7 days: Abdominal Belly pain; Burping/Belching; Choking when eating; Difficulty swallowing; Refusal to eat; Vomiting/Regurgitation. Participants and/or Parents/guardians will assess severity using a scale for 1 (not at all severe) to 7 (most severe). An individual score for each symptom (ISS) will be calculated by finding the product of the number of times a symptom occurred (frequency) and the severity (1-7) in the previous 7 days. Composite symptoms score (CSS), which defined as the sum of the ISSs, will be calculated. This questionaire will be completed weekly and submitted via REDCap.

The primary outcome to assess safety (adverse event score) of PPI therapy will be scores from a questionnaire comprised of 7 respiratory symptoms: upper respiratory infection (cold); sore throat; strep throat; bronchitis; pneumonia; ear infection; acute sinusitis (sinus infection) (See figure 7 in appendix). The PI and his team have experience using this questionnaire to evaluate the safety of lansoprazole treatment in children(17). The prevalence of each respiratory symptom will be compared in participants receiving genotype-driven dosing. Additionally, the doses of PPI will be compared.

In addition, each month, parent/legal guardian(s) and/or study participant(s) will briefly answer questions regarding the impact of gastrointestinal and sinus and/or nasal problems on the child's quality of life. Gastrointestinal problems such as: stomach pain and hurt; stomach upset; food and drinks limits; trouble swallowing; heartburn and reflux; gas and bloating; constipation; diarrhea; worry; medicines and communication will be measured. On the other hand; sinus infection; nasal obstruction; allergy symptoms; emotional distress; activity limitations and overall quality of life are some of the metrics to be evaluated for sinus and/or nasal problems. Each metric has its own scoring scale. Gastrointestinal problems will range from 0-100 for "Never" to "Almost always", respectively. Sinus and/or nasal problems have a 1-7 scale for "None of the time" to "All of the time", respectively.

Inclusion Criteria. The goal of this pilot is that it be pragmatic and parallel routine clinical practice. This is important because we expect that the results of our trial to be readily generalizable and that this be implemented in a routine clinical setting. The goal of patient selection is to enroll 120 children, between the ages of 2 and 17 years, with GERD or other stomach acid mediated conditions for which a PPI is prescribed. Participants must be either currently under a Proton Pump Inhibitor (PPI) therapy or will start a PPI therapy. Eligible participants must have access to internet and a valid email adress to comply with weekly study surveys to be completed online.

Exclusion Criteria. This study will exclude children who have had peptic ulcer surgery; with a history of PKU; with a history of previous adverse effects from PPI treatment or a sensitivity to aspartame (NutraSweet, Equal); who are non-adherent including inability or unwillingness of the legal guardian to provide consent or unwillingness of the child to provide assent; who are unable to take study medications; who are unable to communicate via telephone or other device; who do not have access to a computer with internet access.

V. **FACILITIES REQUIRED/PHYSICAL LOCATION OF STUDY** *(Specify the facilities to be used for the conduct of the proposed research and extent of availability to the project. List the most important equipment items required for this project, noting the location and availability of each)*

Nemours Children's Hospital-Orlando, FL:

NCH has a fully equipped General Clinical Research Center (GCRC) on the 4th floor of NCH, supported by dedicated clinic rooms and inpatient rooms as required for research studies, and with additional space for equipment, supplies, staff and other resources. In addition, NCH maintains a GCRC at NCH's Clinic at 1717 Orange Avenue in Orlando for patient visits at that Clinic. The research effort is supported by the Pathology Department, whose resources include state-of-the-art testing facilities, as well as a newly acquired BD BioSciences FACSCanto II flow cytometer.

NCH leases over 2,000 sq. ft. of laboratory and office space for its biomedical research projects located at the Sanford Burnham Medical Research Institute. NCH also leases over 4,000 sq. ft. of laboratory and office space at the UCF College of Medicine's Burnett School of Biomedical Sciences. With ample room to expand its activities as necessary, NCH houses its Offices of Clinical Research and Sponsored Projects at the CoM.

Clinical:

NCH is a state-of-the-art 137-bed free-standing Children's Hospital in the Lake Nona Medical City region of Orlando, with robust satellite clinics in downtown Orlando, Viera, Lake Mary, and CMS sites throughout greater Orlando. The Nemours Division of Gastroenterology has currently has 7 providers: 4 physicians, 3 Nurse Practitioners and 3 full time registered nurses with plans to expand to 6 physicians in 2015 who will all assist in

patient recruitment. NCH has a Medical Staff of 120 physicians and 50 mid-level providers at NCH. Staff provides services to our affiliated sites, with close to 50,000 office-based encounters in 2012. The NCH outpatient center has 8 fully-equipped patient rooms, and a >2000 sqft family education and media center call Kidstrack, specifically dedicating to teaching families about health.

The NCH Division of gastroenterology has a state of the art pediatric endoscopy laboratory with full endoscopic capabilities, capsule endoscopy, breath hydrogen testing and pH-impedance (PH-MII) probe testing. GI Procedures are performed in the inpatient hospital, the operating rooms, special procedure rooms and the Hospital Outpatient Division (HOD). PH-MII analysis is performed on the 4th floor HOD area in the NCH GI laboratory using the ZepHr/ Z/pH recorder, calibration kit, laptop computer and printer. Specific to this project, our team has extensive experience with single use Z/pH catheters (external reference) that can assess 24 hour acid and nonacid gastroesophageal reflux and gastric pH in patients from birth to adulthood (Sandhill Scientific). Dr. Roberto Gomez is the Director of the NCH GI Laboratory who supervises the registered nurses and GI technicians all with specialized training in pediatric gastroenterology.

Nemours Children's Hospital Orlando houses two Spartan RX point-of-care (POC) platforms in the Pathology Lab. The instruments will be supervised by Dr. Kamran Badizadigan, Chief of Pathology and Director of the CLIA approved Clinical Lab. The Spartan RX CYP2C19 system is capable of genotyping *2, *3, and *17 alleles in parallel from a single patient's buccal swab with a prep time of 4 min and a run time of 60 min. The Spartan RX is reported to have a specificity of 100% and a first-pass call rate of >98% for CYP2C19 *2, *3, and *17 alleles.

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