Num	Title	Authors (presenter in bold) & Affiliation	Abstract
1	The Musculoskeletal Atlas Project (MAP): An anatomical and functional population model of the musculoskeletal system	**Besier, Thor, University of Auckland, NZ;** Zhang, Ju, University of Auckland, NZ; Sorby, Hugh, University of Auckland, NZ; Clement, John, University of Melbourne, Australia; Thomas, David, University of Melbourne, Australia; Lloyd, David, Griffith University, Australia; Nielsen, Poul, University of Auckland, NZ Taylor, Mark, Flinders University, Australia; Hunter, Peter, University of Auckland, NZ Besier, Thor, University of Auckland, NZ; Zhang, Ju, University of Auckland, NZ; Sorby, Hugh, University of Auckland, NZ; Clement, John, University of Melbourne, Australia; Thomas, David, University of Melbourne, Australia; Lloyd, David, Griffith University, Australia; Nielsen, Poul, University of Auckland, NZ Taylor, Mark, Flinders University, Australia; Hunter, Peter, University of Auckland, NZ	In silico testing of medical devices for the musculoskeletal system relies on the ability of computational models to predict outcomes. This, in turn is dependent on capturing key anatomical features and describing appropriate loads and boundary conditions. Image-based subject-specific models of the musculoskeletal system are capable of accurately estimating in vivo joint loads and show promise for clinical use. However, creating subject-specific models is time-consuming and requires high levels of expertise. Also, there is often a 'disconnect' between models used to investigate mechanics and rigid body models to estimate muscle forces. To address these issues, we have developed the Musculoskeletal Atlas Project (MAP), an anatomical and functional atlas of the musculoskeletal system. Our aim is to produce a tool to rapidly generate subject-specific models for computational modelling. We created a python-based software platform (the MAP Client) to facilitate segmentation and meshing of musculoskeletal structures. Users specify their 'workflow' using a drag-and-drop interface and a simple plug-in architecture facilitates customisation and community engagement. Active Shape Models derived from large image datasets guide the segmentation or scale existing mesh templates to match experimental data. The initial anatomical population was derived from 320 clinical CT scans (the Melbourne Femur Collection) and includes surface meshes of the major lower limb bones and muscles. The mesh fitting method deals with sparse data and ensures anatomically feasible solutions when scaling a template mesh to match markers from motion capture. The subject-specific meshes exported from the MAP Client can be re-meshed for mechanics simulations or used to create anatomically detailed OpenSim musculoskeletal models. Medical imaging data can be saved along with the resulting models in the MAP Database, which is built on the Physiome Repository (models.physiomeproject.org). The web-based MAP Database supports access control, version tracking, and facilitates annotation and searching via the MAP Query tool. Our long-term vision is to foster a community of MAP users to accelerate the clinical use of computational models and implement a framework for in silico virtual testing of medical devices.
2	Adaptive Enrichment Designs for Randomized Trials with Delayed Endpoints, using Locally Efficient Estimators to Improve Precision	**Rosenblum, Michael, Johns Hopkins Bloomberg School of Public Health;** Qian, Tianchen, Johns Hopkins Bloomberg School of Public Health; Du, Yu, Johns Hopkins Bloomberg School of Public Health; Qiu, Huitong, Johns Hopkins Bloomberg School of Public Health;	Adaptive enrichment designs involve preplanned rules for modifying enrollment criteria based on accrued data in an ongoing trial. For example, enrollment of a subpopulation where there is sufficient evidence of treatment efficacy, futility, or harm could be stopped, while enrollment for the remaining subpopulations is continued. Most existing methods for constructing adaptive enrichment designs are limited to situations where patient outcomes are observed soon after enrollment. This is a major barrier to the use of such designs in practice, since for many diseases the outcome of most clinical importance does not occur shortly after enrollment. We propose a new class of adaptive enrichment designs for delayed endpoints. At each analysis, semiparametric, locally efficient estimators leverage information in baseline variables and short-term outcomes to improve precision. This can reduce the sample size required to achieve a desired power. We propose new multiple testing procedures tailored to this problem, which we prove to strongly control the familywise Type I error rate, asymptotically. These methods are illustrated through simulations of a trial for a new surgical intervention for stroke.

3	Timeliness of Digital Media Surveillance for Early Warning Detection of Food Contamination in China	**Bao, Wenjie, Epidemico**; Aman, Susan, Epidemico; Freifeld, Clark, Epidemico; Brownstein, John, Epidemico; Anema, Aranka, Epidemico	**Introduction**: The Food and Drug Administration (FDA) is building a novel digital surveillance platform to monitor risk of contamination in the food supply chain. We report preliminary findings from the pilot system, focusing on the supply chain from China to the United States (U.S.). **Methods**: Data were acquired using search terms embedded in RSS feeds from Google (Chinese and English) and Baidu News. Data acquired between August 1 2014 and March 20, 2015 were manually curated by an analyst. Meta-data regarding contaminant (defined by CDC, FDA), food category (defined by Codex Alimentarius) and event location were auto-populated or manually labeled. Wilcoxon signed rank test was used to perform a time-lag analysis, comparing timeliness of digital and official reports of food contamination events. **Results**: Over the study period, the system collected an average 92 alerts/day, totaling 18,438 alerts indexed and archived. Of all reports acquired by the system, 3422 (18.6%) were manually curated. The most common food contaminants were: Salmonella (880); "Bacteria (unspecified)" (740); and Listeria (695). Food categories most affected by contamination included beverages (2488); fruits and vegetable, seaweeds, nuts, seeds (426); and bakery ware (388). Chinese provinces with the highest number of food safety alerts were Beijing (1413), Guangdong (871) and Shandong (549). Over the study period, a total of 67 food safety alters posted by the National Food Quality Supervision and Inspection Center (NFQS) were identified and matched to digital alerts captured by the pilot system. After removal of duplicates, a total of 59 articles were included in the study. 55 (93%) of them were acquired and reported in our system earlier than NFQS. The average time lag by NFQS is 1.627 days (95% CI: 1.004, 2.250). Wilcoxon signed rank test with continuity correction: V = 935.5, p-value = 1.537e-06 **Discussion**: Results demonstrate the utility of digital surveillance for detection of food safety risks in products originating in China. Follow-up studies are required to evaluate risks posed to U.S. consumers.
4	HealthMap: Digital Disease Detection	**Bahk, Chi, Epidemico**; Freifeld, Clark, Epidemico; Aman, Sue, Epidemico; Brownstein, John, Epidemico	HealthMap (www.healthmap.org) is a freely accessible, automated online information system tracking emerging diseases for a diverse audience, from public health officials to international travelers. Operating since 2006, HealthMap continually aggregates reports on new and ongoing infectious disease outbreaks globally in 15 languages. The system collects and integrates outbreak data from over 50,000 informal sources (e.g. news reports, validated personal accounts) and formal sources (e.g. WHO, OIE, FAO). . Through the use of text processing algorithms, the system classifies alerts by location and disease and then displays them on an interactive geographic map. Human analysts curate the alerts to further improve the accuracy. HealthMap detects common, seasonal or endemic conditions as well as outbreak and epidemic situations, and has been credited with efficient, early detection of new and recurrent infectious disease outbreaks. Specifically, during the 2009 H1N1 swine flu pandemic, HealthMap detected early informal reports from a local news source in Mexico reporting "mysterious" influenza-like illnesses, which was retrospectively identified to be the earliest report of this pandemic. Further, informal media sources also tracked the spread of this pandemic from La Gloria, Veracruz, Mexico, to other parts of Mexico including Oaxaca, Baja California, and Mexico City, and eventually to San Diego. Most recently, for the largest recorded outbreak of Ebola ongoing as of March 2015, HealthMap picked up the earliest public signals of initial outbreak in Guinea dating back to March 2014, nine days earlier than official sources. Since then, it continues to monitor the Ebola outbreaks, and displaying on an interactive online tool created to track and visualize the disease's spread temporally and geographically. This tool includes analysis of case and mortality data along with information on social disruption and control strategies. Within 6 months of the outbreak more than 13,000 alerts had been aggregated, classified, and visualized (www.healthmap.org/ebola).

5	MedWatcher: Digital Tools for Post-Marketing Surveillance	**Pierce, Carrie**, Epidemico; Rodriguez, Harold, Epidemico; Freifeld, Clark, Epidemico; Brownstein, John, Epidemico; Dasgupta, Nabarun, Epidemico	MedWatcher (www.medwatcher.org) is an online tool that addresses the problem of adverse event (AE) underreporting via crowdsourcing and social media listening. To encourage direct user reporting, the MedWatcher App was developed in partnership with the FDA Center for Devices and Radiologic Health. It provides a streamlined Web and mobile reporting form for use by the public and healthcare providers. To date, there are more than 8000 registered users and almost 2000 AE reports have been submitted to the FDA through MedWatcher. To further amplify patient voice in drug safety, MedWatcher Social was developed in partnership with the FDA Office of the Chief Scientists for social media listening and analytics. Public conversations about drugs, devices, and vaccines on Twitter, Facebook, and patient forums are collected and processed via natural language processing and machine learning algorithms, then visualized on a real-time interactive dashboard. Vernacular language, characteristic of these data sources, is translated to MedDRA regulatory language for use by regulatory scientists. Initial validation studies have shown statistically significant correlation (ρ=0.75) between Twitter posts describing possible AEs and voluntary reports received by FDA.
6	The Arkansas Research Consortium in Nanotechnology: A Partnership with the FDA National Center for Toxicological Research Focused on Environmental Health & Safety Effects of Graphenes	**Buchanan, Roger Arkansas Research Alliance**; Barbote, Ravi; Erf, Gisela; Faouri, Radwan; Henry, Ralph; McNabb, David and Salamo, Greg, University of Arkansas; Biris, Alex and Bourdo, Shawn University of Arkansas at Little Rock; Basnakian, Alex; Fahmi, Tariq; Nedosekin, Dmitri and Zharov, Vladimir University of Arkansas for Medical Sciences	State universities and federal institutions often collaborate on projects. The State of Arkansas and FDA formalized this process with a Memorandum of Understanding, and established a Research Consortium in Nanotoxicity (ARCN) in 2011 to provide leadership in assessing risks associated with nanotechnology. Five Arkansas universities have pooled research capabilities in nanotechnology with FDA's NCTR to provide the FDA with data, methods, and the tools needed to evaluate potential environmental, health and safety effects of commercially available, custom synthesized and functionalized graphenes. Graphene is a form of carbon consisting of nanoscale sheets of sp2-hybridized carbon. These structures have been touted as platforms for many applications including drug delivery or implantable microelectronics. Graphene presents a significant challenge for detection and quantification in biological systems, and if administered into humans, would be extremely difficult to detect Current work on this project include: 1) Use of a wide variety of analytical techniques for characterizing physical and chemical properties of commercially available and custom synthesized graphenes with special emphasis on understanding surface chemistry and interaction with cell membranes; 2) Evaluation of contaminants and endotoxin content in commercially available graphenes; 3) Development of graphenes containing intercalated metal ions to enhance detection in biological matrices; 4) Development of methods for controlled functionalization of graphenes; 5) Use of advanced photoacoustic and thermal imaging systems to detect, measure and track graphenes in vitro and in vivo; 6) Development of eukaryotic and prokaryotic systems for genome wide studies of potential toxicological impacts of exposure to graphenes; 7) Characterization of impacts of exposure to graphenes on immune system responses, endothelial cells and neural development; 8) Exploration of the efficacy of using technologies of assessing alterations in DNA structure to investigate potential impacts of exposure to graphenes. These projects will inform the FDA and other regulatory agencies on the methods associated with characterization and purity assessment of graphenes, and biological properties of this nanomaterial.

7	Advancing Continuous Flow Reactor Technology through Real-Time Control and Product Isolation for Improved Quality Assurance and Consumer Safety	**Dearing, Thomas, MarqMetrix Inc**; J Mark Weller , MarqMetrix Inc; Charles W Branham, MarqMetrix Inc; Brian J Marquardt, MarqMetrix Inc;	Currently, the majority of pharmaceuticals is performed in large volume batch reactors. Batch reactors have inefficient mixing, poor temperature stability and pose significant risks to operators. In addition, ensuring in real-time that the material being produced are correct is difficult due to large reactor volumes and heterogeneous material distribution. Many of these problems are mitigated by using continuous flow reactors (CFR's). CFR's are closed reaction systems comprised of highly configurable reactor plates that integrate efficient mixing and temperature control jackets. When the reactors are outfitted with sampling interfaces, process analytical technology can be employed to make real-time measurements of the material being produced and enable control of a system. A major drawback of CFR's is the degree to which a user must provide control. Current CFR's rely on experimentation to discover the optimal reactor conditions. These experiments are costly and time consuming, and reduce the average production volume per year. Samples still need to be collected into larger volumes for product isolations, such as solvent exchanges. This limits the fully continuous nature of the process. A secondary drawback is the overhead on each system that is associated with expanding reactor output. Scaling out of a CFR system to multiple locations could become cost prohibitive due to the computing and software licensing costs, model maintenance and overheads. To overcome these drawbacks we have undertaken four phases of research. Phases 1 & 2 address the amount of input required from a user by building a series of dynamic models that will automate and optimize the reactor. Phase 3 addresses the bottleneck of production associated with product isolation. Phase 4 will aim to mitigate the overhead associated with scaling out CFR systems. We intend to demonstrate scaling out of a CFR through microcomputers and cloud based communication and analysis. We expect this research aid in the increased adoption of continuous flow technology. Phase 1 was completed on 3/17/2015 the models generated predicted the final yield of material with an error of ±3.680%.These models can be automated and control the reactor to ensure that the final material is safe and within specified guidelines.

8	Variations in the Physical Characteristics of Generic Drugs and Patients' Perceptions: Surveys of Pharmacists and Patients	**Dutcher, Sarah**, Office of Research and Standards, Office of Generic Drugs; Kesselheim, Aaron, Harvard Medical School/Brigham and Women's Hospital; Gagne, Josh, Harvard Medical School/Brigham and Women's Hospital; Sarparwari, Ameet, Harvard Medical School/Brigham and Women's Hospital; Fulchino, Lisa, Harvard Medical School/Brigham and Women's Hospital; Avorn, Jerry, Harvard Medical School/Brigham and Women's Hospital; Campbell, Eric, Harvard Medical School/Massachusetts General Hospital Jiang, Wenlei, Office of Research and Standards, Office of Generic Drugs	**Background**: Generic drugs are required to be pharmaceutically equivalent and bioequivalent to their brand-name reference drugs, but may differ in their physical appearance (e.g., color, shape, size, markings). How differences in appearance between therapeutically equivalent products create or reduce patient confusion, affect patient medication adherence, or are handled by pharmacists is unknown. **Objective**: To conduct a survey of pharmacists and two surveys of patients regarding their perspectives on and experiences with generic drugs that differ in appearance from previous fills of the same medication. **Methods**: The pharmacist survey will be mailed to a nationally-representative sample of U.S.-licensed pharmacists practicing in community pharmacy settings. The first patient survey will be conducted via telephone and will target patients 50 years or older who are taking one or more generic medications for one of six chronic conditions: epilepsy, diabetes, hypertension, hyperlipidemia, depression, and HIV. The second patient survey will be mailed to adults in the Optum Research Database identified as taking one of four pre-specified generic drugs for a chronic condition and recently experiencing a change in the appearance of that medication. Pharmacist and patient surveys each have a goal of 1000 respondents and will cover parallel topics, including: knowledge about the bioequivalence of generic drugs, pharmacist involvement in managing pill appearance changes, confidence in the safety and effectiveness of pills with differing appearance, patient outcomes with appearance changes, and respondent demographic information. All surveys are expected to be completed less than 20 minutes. **Accomplishments to date**: The surveys were developed based on environmental literature scans and input from an expert survey panel and FDA's Office of Generic Drugs. All surveys are in the final stage of development and are undergoing OMB approval as information collection under the Paperwork Reduction Act of 1995. **Implications**: These surveys will further understanding about the relationships between changes in pill appearance and patient outcomes such as adherence and how pharmacists manage these changes. The results from these surveys will be used by FDA to inform the development of educational programs and policies, and to determine actions needed to promote safe use of generic medicines with varying appearances.
9	Sub-visible Particles of Intravenous Immunoglobulin (IGIV) Induce Innate Immune Response in PBMC, primary monocytes and THP-1 cells	**Moussa, Ehab, Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN;** Kotarek, Joseph, Center of Biologics Evaluation and Research, US FDA, Silver spring, MD; Marszal, Ewa, Center of Biologics Evaluation and Research, US FDA, Silver spring, MD; Blum, Janice, Department of Microbiology and Immunology, Indiana University School of Medicine; Topp, Elizabeth, Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN	**Purpose**: To investigate the effects of aggregates of intravenous immunoglobulin (IGIV) on the innate immune response in vitro, and to develop a well-define human cell-based system to screen formulations for potential immunogenicity. **Methods**: IGIV aggregates were prepared by various pharmaceutically relevant accelerated stress methods. Stressed samples were characterized for particle size, count and higher-order structural changes. Immune cell activation tracked by inflammatory cytokine release in response to aggregates in vitro was evaluated using peripheral blood mononuclear cells (PBMC) and primary monocytes from healthy volunteers, as well as two myeloid-derived immortalized cell lines: THP-1 and Monomac 6 (MM6). **Results**: IGIV aggregates produced by mechanical stress (shaking or stirring) induced higher cytokine release by PBMC and primary monocytes than aggregates formed by other stresses. THP-1 cells showed trends similar to primary monocytes. Effects in both primary monocytes and THP-1 cells were dose-dependent and partially inhibited by blocking toll-like receptors 2 and 4 (TLR2 and TLR4). **Conclusions**: IGIV aggregates induce a dose-dependent inflammatory cytokine response in PBMC, human monocytes and THP-1 cells, mediated in part by TLR2 and TLR4. Additionally, THP-1 cell-line can be useful to model innate immune response of PBMC to screen for immunogenicity of IgG aggregates.

10	Medical Device Innovation Consortium (MDIC) Case for Quality	**Fiorino, Suzanne, Medical Device Innovation Consortium (MDIC) & Johnson & Johnson Medical Devices** Garth Conrad, Medtronic Sarah Deegan, Johnson & Johnson Global Orthopedics Joanna Engelke, Boston Scientific Donna Godward, Johnson & Johnson Medical Devices Bill Murray, Medical Device Innovation Consortium (MDIC) Joseph Sapiente, Medtronic Steven Solomon, Food & Drug Administration (FDA) Francisco Vicenty, Food & Drug Administration (FDA) Jan Welch, Food & Drug Administration (FDA)	The Medical Device Innovation Consortium (MDIC) has implemented research and established a Forum, in support of the FDA Case for Quality (launched in 2011), to serve improved healthcare for patients. MDIC has received funding under BAA HHSF223201400155C to establish such a forum and continue this Case for Quality collaboration. Dedicated to improving medical device quality and safety for patients, MDIC Case for Quality is focused on creating a Collaborative forum with broad participation of public and private stakeholders to promote the concepts of regulatory science tools, methods, and approaches to: 1. Understanding of medical device quality, its importance to innovation (product, process) and contribution to improved healthcare outcomes 2. Transparency and information exchange between stakeholders (regulators, providers, patients, industry, and others) 3. Collaboration with FDA in understanding the challenges and technology advancements for consideration of evolving regulatory models The MDIC Case for Quality work - will deliver the following: 1. Conducting research on Maturity Models and producing a report on the what Maturity Models could potentially be used in the Medical Device industry 2. Develop and implement a schedule of both closed participant only sessions and open-to-the-public meetings for the purpose of discussing key areas of improvement needed for the Medical Device industry. Charter projects aimed at fixing prioritized issues identified by the Forum. Oversee the portfolio of projects undertaken by stakeholder groups to ensure development of and improvement of key quality metrics. 3. Developing a Change Action Plan to detail out actions required to advance the Case for Quality either via adopting a Maturity Model or other actions as identified during the Forum meetings. Currently research is being conducted on Maturity Models, the First Forum has been conducted, and plans are in place to conduct subsequent Forums.

11	Systematic Risk Assessment of Human Exposure to Tobacco Products using Computational Models	**Kitani, Takashi, PointCross, Inc.**; Tran Ho, Lam Thuy Vi, PointCross, Inc.; Madhavan, Suresh, PointCross, Inc.; Nath, Shree, PointCross, Inc.; Sadashivaiah, Prasanna, PointCross, Inc.; Erkkila, Brian, FDA/CTP; Chemerynski, Susan, FDA/CTP; Yeager, Phil, FDA/CTP; Nguyen, Luc/ FDA/CTP; Jackson, Habibah, FDA/CTP; Sholtes, Deborah, FDA/CTP	A strategic priority for CTP is to continue to establish and meet performance standards for tobacco product reviews. There are several refinements that could assist in meeting these performance standards while maintaining the scientific rigor necessary for the protection of public health, including improving regulatory reporting, standardizing Harmful and Potentially Harmful Constituent (HPHC) listings , and developing more efficient systems for evaluating submissions. To meet these important regulatory and scientific needs, CTP engaged with PointCross, Inc. through a Broad Agency Announcement (BAA) initiative in 2014 in order to collaboratively build a Risk Modeling and Simulation Tool (RMST). The RMST allows for systematic assessment of health risks associated with human exposure to tobacco products through the use of computational models and advanced visualization. Within the tool, CTP Toxicologists may define, edit, store, and specify parameters for multiple tobacco cancer risk models. These parameters include: a) Smoker characteristics, b) HPHC properties, c) HPHC concentrations, and d) Cancer risk algorithms. In addition, regulatory toxicologists may access pre-defined models to run multiple cancer risk assessments of tobacco products and dynamically assess visual representation of the data. Further, comparisons may be made between different types of tobacco products and different types of predictive models. The tool enables visual analysis of the executed model, supplemented with tabulated data summaries, and generates reports for regulatory reporting purposes. Future development of RMST will support larger sets of variables to describe a range of carcinogenicity risks using stochastic simulations. Since such simulations will generate large data volumes that must be stored, post-processed and summarized for CTP use, the tool is being built using the Hadoop platform, which provides the scalability and robustness necessary to meet CTP's long-term needs. CTP scientists have reviewed the initial version of the RMST. Based on this initial review and ongoing development, it is expected that in the future, the tool will contribute to CTP's strategic priority to meet performance standards for tobacco product reviews while maintaining the scientific rigor necessary for the protection of public health.
12	The Diversity Outbred: A tool to Improve Preclinical Safety Testing and Pharmacogenomic Analysis	**Harrill, Alison, University of Arkansas for Medical Sciences** Lyn-cook Jr., Lascelles, University of Arkansas for Medical Sciences Gatti, Daniel, The Jackson Laboratory Churchill, Gary, The Jackson Laboratory	Hepatotoxicity is a major cause of attrition during pharmaceutical development. Newer models have offered improvements in predicting incidence of common (high frequency) hepatotoxic events, yet the ability to detect idiosyncratic (low frequency) drug-induced liver injury (DILI) has remained elusive. While rodent models involving external or internal manipulation have enabled mechanistic study of certain drugs, there remains a need for an animal model that can detect liver liabilities where the mode of action is unknown. A critical issue is that conventional models lack genetic diversity, which in several instances has been shown to play a role in adverse drug reactions. The Diversity Outbred (DO) mice comprise a genetically diverse population with variability that surpasses that of the human population, but in which the minor allele frequency is greater in the DO (12.5% on average). We hypothesized that the DO could provide a surrogate model for low frequency DILI in patient populations. In this study, female DO mice (N=50/group) were administered orally one of three drugs associated with rare liver toxicity that are still used clinically (diclofenac, zileuton, isoniazid) or 0.5% methylcellulose vehicle. Mice were dosed (i.g.) daily up to 14 days and blood samples were taken before dosing and at necropsy. As a group, diclofenac and zileuton both caused significant elevations in alanine aminotransferase (ALT) from the pre-dose (baseline) values at necropsy ($P<0.05$). ALT was not elevated by 0.5% methylcellulose ($P>0.05$). Fold elevations in ALT ranged from 0.2-8.3 fold for diclofenac and from 0.2-13.6 fold for zileuton, and group mean±SEM for diclofenac and zileuton post-dosing were 82.8±7.3 U/L and 123.8±10.0 U/L, respectively, compared to 32.39±5.4 U/L in the vehicle group. While preliminary, the data provide an important first step to qualifying the DO mouse population as a tool for improved prediction of rare safety liabilities that may call for personalized prescribing strategies.

13	Research to Mitigate a Shortage of Respiratory Protection Devices during Public Health Emergencies	Harnish, Delbert, Applied Research Associates; Mills, Devin, Applied Research Associates; Lawrence, Caryn, Applied Research Associates; **Heimbuch, B.K., Applied Research Associates.**	In the event of a pandemic influenza outbreak, a shortage of respiratory protection devices (RPDs) is expected to occur. To mitigate a shortage, many agencies have suggested decontamination and reuse strategies for N95 filtering facepiece respirators [FFRs]), and/or using reusable half mask elastomeric respirators (HMERs) and powered air purifying respirators (PAPRs). Our research is focused on both strategies by 1) performing an expanded evaluation of an ultraviolet germicidal irradiation (UVGI) decontamination method we previously developed for N95 FFRs, and 2) evaluating the effectiveness of established cleaning and disinfecting protocols for HMERs and PAPRs. Building upon our past research that showed UVGI could achieve a four-log reduction in viable influenza, we evaluated the method using 1) multiple soilings to simulate virus protective factors (artificial skin oil, artificial saliva), 2) more FFR models, 3) greater number of decontamination cycles, and 4) technology transition into hospitals. A UVGI exposure chamber was used to treat FFR coupons inoculated with H1N1 influenza and covered with various levels of contaminants with multiple UV dosages. Preliminary testing has shown a UV dosage of 1 × 106 mJ/cm2 yields no detectable viable virus (4.0 – 5.0 log reduction) in the absence of contaminants. When soiled by either artificial skin oil or artificial saliva, the same UV dosage demonstrates at least a 3-log reduction in influenza viability. Testing at lower UVGI doses yields lower decontamination efficiency for all conditions. For HMERs, the reusable RPDs were inoculated with H1N1 influenza on five different surface types, covered with soil simulants, cleaned and disinfected according to OSHA protocols, then sampled to determine remaining viable virus. Initial results demonstrated no detectable virus (3.0 – 4.5 log reduction) was recovered from both cleaned HMERs and cleaned and disinfected HMERs for all five surfaces. These data indicate the disinfection step may not be required. We are in the early stages of research, but the results indicate that UVGI is an effective decontaminant of influenza, even in the presence of soil simulants. Additionally, cleaning and disinfecting protocols for HMERs have been shown to be equally effective at reducing the presence of viable influenza on the RPD.
14	Analyzing subvisible protein aggregates in biologics	**Panchal, Jainik, Purdue University**; Marszal, Ewa, Center for Biologics evaluation and Research; Kotarek, Joseph, Center for Biologics Evaluation and Research; Topp, Elizabeth, Purdue University	**Purpose**- Protein aggregation decreases therapeutically available protein and can cause life threatening immunogenic reactions. While many methods are available to characterize and quantify protein aggregates, none is applicable over the relevant size range and different methods often give conflicting results. The studies presented here compare two such methods: dynamic light scattering (DLS) (90° and 173°) and resonance based mass measurement (RMM). **Methods**-Various dilutions of NIST approved monodisperse polystyrene (PS) particle standards of (20, 60, 100, 200, 400 and 1000 nm) were analyzed as monodisperse solutions and as binary mixtures. 5mg/ml IgG in PBS buffer (10mM, pH 7.4) was analyzed after thermal treatment for 2,8 or 24 h. These samples were diluted to demonstrate the effect of dilution on instrument response. 100 mg/ml IgG in 25mM glycine buffer (pH 4.2) was examined similarly. Malvern Zetasizer (90° and 173°) and Archimedes Particle Metrology System (Affinity Biosensors, CA) were used for all the analyses. **Results**- For the particle size standards, the Z-average diameter was underestimated by DLS for the most concentrated samples and overestimated for the most dilute samples at every particle size. Errors in particle size measurement increased with increase in particle size. Based on the results, a working range of concentration was established at which DLS provided an acceptable estimate of particle size. DLS-173° had a better working range than 90°. Binary mixtures were also analyzed to evaluate resolution. Upon analysis of thermally treated 5mg/ml IgG and 100mg/ml IgG samples at various dilutions, smaller aggregate species present in higher concentration were detected using DLS. RMM was able to determine concentration of different species that could be confirmed by dilution. **Conclusion**- The studies reported here compared DLS 90°, DLS 173° and RMM using solutions of monodisperse particle size standards, binary mixtures of particle size standards and aggregated protein solutions to evaluate the effect of concentration and particle size on their measurement ability. The working range of DLS depends on both concentration and particle size.

15	Monitoring changes in aggregate morphology of alpha-1-proteinase inhibitor (A1PI) using hydrogen/deuterium exchange mass spectrometry (HDX-MS) and covalent label mass spectrometry (CL-MS)	**Panchal, Jainik, Purdue University;** Marszal, Ewa, Center for Biologics evaluation and Research; Kotarek, Joseph, Center for Biologics Evaluation and Research; Topp, Elizabeth, Purdue University	**Purpose**- The morphology of protein aggregates may depend on the type of stress, and may ultimately elicit differences in immune response. . Here, hydrogen deuterium exchange (HDX-MS) and covalent labeling (CL-MS) are used as high-resolution techniques to characterize aggregate morphologyfor alpha-1-proteinase inhibitor (A1PI) . **Methods**- 10 mg/mL A1PI (provided by CBER, FDA) was subjected to thermal stress at elevated temperature (55˚C) and pH stress by changing the pH to 4 using sodium acetate buffer to form aggregates. For HDX-MS, 2 µL of the stressed sample was diluted with 18 µL of D2O buffer, pD 7.4 and pulse labeling was carried out for 2 min. The reaction was quenched by decreasing the pH to 2.5 and immediate flash freezing in liquid nitrogen. At the time of analysis, samples were thawed and analyzed immediately using LC-MS (QTOF 6520, Agilent Technologies) equipped with online pepsin column. For CL-MS, samples were labeled for 20 minutes using sulfo-NHS. The labeled protein samples were digested using trypsin/chymotrysin at 60°C for 16 h. Labeled peptides were then analyzed by LC-MS and LC-MS/MS. **Results**- Peptides with sequence coverage of ~90% were obtained by online pepsin digestion of A1PI. These peptides were monitored for changes in deuterium uptake during aggregation. Peptides 248-269 and 342-376 showed a decrease in deuterium uptake for thermal stress suggesting their involvement in formation of aggregates. Following pH stress, peptide 248-269 showed very little change and peptide 342-376 showed an increase in deuterium uptake, while peptide 363-377 showed a decrease. Overall, during pH stress, more peptides are solvent exposed as compared to thermal stress. The results indicate localized differences in solvent exposure of the peptides during aggregation due to differences in aggregate morphology that are captured by HDX-MS. These regions were further probed using CLMS where peptide 258-267 showed less labeling for thermally stressed sample compared to pH stress and unstressed sample. **Conclusion**- A1PI aggregate morphology depends on the type of stress. High-resolution techniques like HDX-MS and CL-MS provides a unique insight into site-specific changes occurring during A1PI aggregation.

16	Analysis of FDA Clinical Trial Data to Improve the Assay Sensitivity and Informativeness of Analgesic Clinical Trials	**Patel, Kushang, University of Washington**; Dworkin, Robert, University of Rochester; Gewandter, Jennifer, University of Rochester; McDeromott, Michael, University of Rochester; Smith, Shannon, University of Rochester; Turk, Dennis, University of Washington	The mission of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the FDA is to identify, prioritize, sponsor, coordinate, and promote innovative activities—with a special interest in optimizing clinical trials—that will expedite the discovery and development of improved analgesic, anesthetic, and addiction treatments for the benefit of public health. A key research objective of ACTTION is the development of an evidence-based approach to the design of analgesic clinical trials. In October 2014, ACTTION was funded through a Broad Agency Agreement to: (1) access, harmonize, and pool raw patient-level data from Phase 2 and 3 acute and chronic pain trials in the FDA's Document Archiving, Reporting & Regulatory Tracking System; (2) analyze patient and study design factors associated with assay sensitivity and placebo group response in patient-level and pooled raw data; (3) examine issues in the statistical analysis of pain data in clinical trials (eg, treatment of missing data, use of longitudinal data in defining outcomes); (4) evaluate responsiveness of existing primary and secondary outcomes—including different scales, composite and responder measures, and measurement approaches; and (5) develop novel outcome measures for analgesic trials (eg, composite measure of pain intensity and use of rescue analgesics). A recent example of ACTTION's research that examined the effect of variability in the 7-day baseline pain intensity diary on the assay sensitivity of neuropathic pain trials (Farrar et al. 2014) will be presented. Retrospective analyses of data from completed clinical trials of interventions with known efficacy has the potential to provide greater knowledge not only of the benefits of different trial design characteristics and statistical methods but also of the responsivity of various outcome measures, all of which could make clinical development and evaluation of new treatments more efficient. The essence of an evidence-based approach to the design of clinical trials is to first understand the relationships between clinical trial characteristics and trial outcome and then test hypotheses based on that knowledge when designing new trials; such efforts have the potential to expedite the development of improved analgesic treatments and thereby improve public health.

17	Signs, Symptoms, and Existing Patient-Reported Outcome (PRO) Measures in Hospital-Acquired Bacterial Pneumonia (HABP): A Comprehensive Literature Review	**Saretsky Todd**, ICON Clinical Research, LLC, San Francisco, CA, USA; Clifford, Sarah, ICON Clinical Research, LLC, San Francisco; Hoffmann Steven C., Foundation for the National Institutes of Health, Bethesda, MD; Powers John H., Leidos Biomedical Research, Inc., North Bethesda, MD; Talbot George H., Talbot Advisors, LLC, Anna Maria, FL; **Howard, Kellee**, ICON Clinical Research, LLC, San Francisco, CA	**Purpose** No standardized methods exist to measure patient-reported outcomes (PRO) related to Hospital-Acquired Bacterial Pneumonia (HABP). The purpose of this literature review was to identify signs, symptoms, and measurement tools associated with patients' experience of HABP. The results will be used to inform the development of a valid PRO tool for HABP that is consistent with the FDA PRO Guidance. **Methods** To identify relevant literature, MEDLINE (1946 to 2014) and EMBASE (1988 to 2014) databases were searched individually and in combination using terms related to Hospital- Acquired Pneumonia (HAP), HABP, signs and symptoms, and patient reported outcomes. **Findings** The search identified 1384 abstracts. 225 were excluded as duplicates or for missing content. 1145 abstracts were excluded based on pre-specified criteria. The remaining articles were scrutinized for eligibility, resulting in six that met the inclusion criteria. The most frequently cited signs and symptoms of HABP were fever, cough, purulent sputum, dyspnea, rales, chest pain, and elevated respiratory rate. No PRO measures for assessing HABP signs and symptoms were identified in the literature. Current HABP clinical trials have not included end points that directly measure how a patient feels and functions. **Conclusions** The HABP literature has historically focused on clinical outcomes to evaluate treatment efficacy and there is currently limited evidence assessing the impact of antibiotic therapies on symptomatology in HABP patients. Endpoints, such as clinical response, clinical cure, and time to event, are only indirect measures of treatment benefit and have not been validated. It is essential to develop reliable, well-defined and clinically relevant endpoints that measure tangible benefits for patients in clinical trials of antibacterial drugs in accordance with the FDA Guidance for PRO measures and HABP. This literature review is the first step in identifying concepts that will be explored further in qualitative interviews with HABP patients.

18	Sensitivity Analysis of Randomized Trials with Missing Data	**Scharfstein, Daniel**, Johns Hopkins Bloomberg School of Public Health/Department of Biostatistics McDermott, Aidan, Johns Hopkins Bloomberg School of Public Health/Department of Biostatistics	Missing outcome data are a widespread problem in randomized trials. While unbiased estimates of treatment effects can be obtained from trials with no missing data, this is no longer true when data are missing on some patients. The essential problem is that inference about treatment effects relies on unverifiable assumptions about the nature of the missing data mechanism. It is widely recognized (2010 FDA--sponsored NRC report entitled "The Prevention and Treatment of Missing Data in Clinical Trials"; 1998 ICH Guidance document E9; 2009 EMEA "Guideline on Missing Data in Confirmatory Clinical Trials") that the way to address this problem is to posit varying assumptions about the missing data mechanism and evaluate how inference about treatment effects is affected by these assumptions. The NRC report lays out a framework for sensitivity analysis in which a primary analysis is conducted under a reasonable benchmark assumption and the robustness of the associated conclusion is evaluated by conducting inferences under assumptions in a large “neighborhood” around this assumption. The purpose of this FDA sponsored project is to: (1) create methods for the sensitivity analysis of randomized trials in which outcomes, scheduled to be measured at fixed points in time after randomization, are missing monotonically or intermittently; (2) develop free and open source software to implement these methods; and (3) demonstrate the methods and software using real clinical trial data. To date, we have developed and implemented flexible methods for conducting sensitivity analysis of randomized trials with monotone missing outcome data. In these methods, “missing at random” serves as the benchmark assumption. An R software package named SAMON has been created and is available at www.missingdatamatters.org. We have illustrated the methods and software using data from three clinical trials. These case studies demonstrate the usefulness of the methodology and software. We are currently in the process of extending the capability of the software to handle intermittent missing data. The methods and software we have developed will help sponsors and regulators more comprehensively assess the robustness of trials with missing data, as per recommendations of the NRC Report and regulatory guidance documents.

21	University of Arkansas for Medical Sciences (UAMS) Regulatory Sciences Training and Research Program – Partnership between UAMS and NCTR	**Gandy, Jay, University of Arkansas for Medical Sciences**; Cranmer, Morris F., University of Arkansas for Medical Sciences	UAMS established a Regulatory Sciences Training and Research Program in 2012 under a Memorandum of Understanding between the FDA and the State of Arkansas. The program is built on long-standing research and graduate training interactions between UAMS and the FDA's National Center for Toxicological Research (NCTR), which is located just 30 mile south of the UAMS campus. To date, the UAMS Regulatory Sciences Program has 1) established a Graduate Certificate in Regulatory Science with 22 students in the inaugural class; 2) hired two new faculty dedicated to conducting research to advance the development of new tools, standards and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products; 3) initiating a fully online Certificate in 2015 that will extend the reach of the program; and 4) received approval for a Master's of Science degree planned for 2016. The Program has 25 graduates, with another 9 students projected to graduate in Spring 2015. A primary goal of the training program is to provide students with insight into the complexities of the laws, regulations, policies, and the underlying scientific studies required for advancing regulatory decisions. Courses are taught by UAMS faculty and lecturers from FDA and private industry. Participating students in the Regulatory Sciences program are NCTR post-doctoral ORISE Fellows and Commissioner's Fellows, UAMS post-doctoral fellows, and UAMS graduate students. The research efforts of the Regulatory Science program are focused on areas devoted to modernizing toxicology to improve medical products safety assessment. The Regulatory Sciences Program has become an integral part of the UAMS Clinical and Translational Science Award (CTSA) Translational Research Institute, which has contributed significant financial resources to the start-up for the two new faculty. The investment has already seen a return of $1.7 million in grants and contracts awarded to these two new investigators. (Supported in part by UL1TR000039 and KL2TR000063)
22	Leveraging Bacteriophages for High Speed, Enrichment-free Environmental Monitoring	Hu, Zonglin, U.S. Food and Drug Administration, Office of Regulatory Affairs/Winchester Engineering and Analytical Center; Michael Koeris, Sample 6/Boston, MA; Jayson Bowers, Sample 6/Boston, MA	Bacterial pathogen detection in food processing and transport environments, as well as in the finished product itself is critical to the security and safety of the food supply chain. Increased emphasis on generating rapid feedback from assay methods enables stakeholders in the food supply chain to act on the data while still being in control of the product, or to minimize the exposure risk of the consuming public. However, existing microbiological tests require between 24-48 hours of enrichment after sample collection and off-site shipping (additional 12-24h), followed by sample preparation, before running an assay - thereby lengthening the feedback cycle unduly and increasing the risk. Sample6 has developed a bacteriophage-based detection system for environmental Listeria contamination with total time to result of less than one shift (<8h). Bacteriophages only produce the reporter in living cells, therefore the user realizes automatic live/dead discrimination as an added benefit. The assay was evaluated in an AOAC setting for inclusivity, exclusivity, robustness, instrument variation, and product consistency and stability, as well as in a method comparison study using an environmental surface. All of the Listeria spp. (55) and exclusivity strains (30) tested were accurately identified. In the comparison test, the Sample6 assay was statistically significantly more sensitive than the USDA MLG reference method, in the presence of 10X competing cells *(Enterococcus feacalis)*. We are in the process of repeating this work in collaboration with the FDA's WEAC by using the BAM method for Listeria detection, as well as evaluating further environmental surfaces and conditions, to broaden the applicability of this assay. These results demonstrate for the first time that an enrichment-free assay has the necessary sensitivity, specificity and robustness to be run within a single shift. This assay is transformative for the food industry, the food supply chain and all actors and stakeholders within it.

23	A Rapid, Multiplexed, Mobile Phone-Enabled Point of Care Diagnostic Device to Detect Category A Bioterror Agents	Tam, Justina, Regan, Patrick and Clavet, Charles, FDA Winchester Engineering and Analytical Center; Yen, Chunwan and Bosch, Irene, FDA ORISE Fellow/Institute for Medical Engineering and Science, MIT, and Department of Microbiology and Immunobiology, Harvard Medical School; de Puig Guixe, Helena and Phillips, Eliza, MIT/SUTD International Design Center, MIT; Institute for Medical Engineering and Science, MIT, and Department of Microbiology and Immunobiology, Harvard Medical School; Miyazaki, Hikaru and Fiegen, Ann, Institute for Medical Engineering and Science, MIT, and Department of Microbiology and Immunobiology, Harvard Medical School; Gomez-Marquez, Jose, Little Devices @ MIT, MIT/SUTD International Design Center, MIT; Hamad-Schifferli, Kimberly, Lincoln Labs, MIT; Gehrke, Lee, nstitute for Medical Engineering and Science, MIT, and Department of Microbiology and Immunobiology, Harvard Medical School.	Medical countermeasures surveillance and reporting during and after a public health emergency event require sensitive and specific detection/diagnostic methods and devices. We are designing, building, and testing a rapid, multiplexed, mobile phone-enabled diagnostic device to detect dengue virus and Ebola virus, Category A bioterror agents, in the field. The goal is to deliver a device that will permit screening for multiple pathogen markers without the need for refrigeration, specialized training, specialized equipment or chemicals. Mobile phone technology is used to analyze the lateral flow data, quantify the results, and upload the results for real time epidemiology. Methods: The device is based on lateral flow chromatography, an established technology. Current multiplexing permits assay for up to eight pathogen markers concurrently using one hundred microliters of sample. Monoclonal antibodies have been screened using flow cytometry and lateral flow chromatography to define functional pairs when conjugated to gold nanoparticles and bound to nitrocellulose paper. Nanoparticle surface chemistries are being evaluated to identify low cost approaches to prepare conjugated nanoparticles. A mobile phone app has been coded to record the image of the multiplexed diagnostic, correct the image for user photography errors, quantify the signal intensities, and upload data to a server, with GIS. Results: A prototype device that detects and distinguishes the four serotypes of dengue virus, dengue IgG/IgM, Ebola glycoprotein, and ST2 protein has been built and tested. Initial specificity and sensitivity tests using laboratory proteins and human patient serum samples are favorable. The phone app records the data, measures signal intensities, and uploads data for real time epidemiology. Conclusion: A multiplexed rapid lateral flow diagnostic for field use detects Category A pathogens and uploads data for real time epidemiology.

24	Measurement Techniques for Conductive Polymer Membrane Based Biosensors	Bandremer, Aaron, Commissioner's Fellow ORA/WEAC; Torosian, Stephen, ORA/WEAC; Goktas, Hilal, ORISE Fellow ORA/WEAC	The conformal thin-film deposition of conducting polymer (CP) via vapor deposition onto a fiber mat is an attractive platform to base an electrochemical biosensor (Bhattacharyya, 2011). The monomer 3-thiopheneethanol (3-TE), with an accessible hydroxyl group, has been successfully co-polymerized with 3,4-ethylenedioxythiophene (EDOT) onto melt-spun fibers utilizing oxidative vapor deposition. The functional groups of the co-polymers are used to covalently attach antibodies to the surface of the platform for binding to targets such as E. coli O157:H7. We compare and contrast electrochemical detection methods utilizing resistance and potentiostat for environmental monitoring. An open-source potentiostat (Rowe, 2011) was constructed for voltammetric techniques to assess the functionalized conducting polymer as the working electrode of a standard three electrode system. Though the electrochemistry of antibody functionalized conducting polymers binding to target antigen does not involve a redox reaction typically encountered in voltammetry, interactions between antibody and antigen induce a capacitance change of the conducting polymer leading to a polarization of the membrane and a detectable signal (Sargent, 1999). We have also explored the traditional redox approach applied to our system. Potassium ferricyanide and ascorbic acid, both commonly used in oxidation-reduction experiments, have been tested in our sensor system. With an increase in the number of bacteria bound to the surface of the membrane, the electrons of the redox couple are inhibited from transfer to the membrane surface, thereby decreasing the peak observed in voltammetry. Resistance based methods (McGraw, 2012) with two point probes have also been shown to be promising detection signals and were evaluated for sensitivity. In addition, a four point probe was evaluated to minimize the effect of contact resistance. However, the four point probe applied to a porous membrane leads to poor measurement reproducibility and is used only as a screening tool for choosing a membrane to incorporate into a biosensor. Both resistive and voltammetric techniques offer sensitive and (near) real time monitoring for environmental assaying of O157:H7. A head to head comparison of both techniques and their ability to be incorporated into a field deployable device was investigated to determine a final configuration.
25	Label-free Chemiresistive Biosensor for Low Level Detection of E. coli	Goktas, Hilal, ORISE Fellow ORA/WEAC - ChemE/MIT; Bandremer, Aaron, Commissioners Fellow ORA/WEAC; Hebert, Amanda ORISE Fellow ORA/WEAC; Torosian, Stephen, ORA/WEAC; Gleason, K. Karen, ChemE/MIT	The Food Safety Modernization Act specifically addresses incorporating technological advances in carrying out the US Food and Drug Administration's (FDA) mission to protect the public. However, even with overall improvements in safety and regulation of food, FDA still conducts considerable numbers of recalls and safety alerts due to foodborne pathogens. Hence, a rapid, cost-effective, and early detection biosensor would be a valuable tool not only for the food industry but also for regulatory bodies. We present new developments in fabrication of a flexible, label free biosensor based on chemiresistive technique for the detection of Escherichia coli (e.g., E. coli O157), responsible for numerous food-borne and water-borne infections worldwide. The biosensor is constructed on a fiber like matrix of melt spun polypropylene (membrane) due to its strength and its high surface area character. It is fabricated by synthesizing chemically sensitive conductive, functionalizable polymeric thin film via oxidative chemical vapor deposition (oCVD) technique to immobilize the analyte detecting molecules. The degree of functionalization versus the bacterial attachment is investigated as well as integration of a wireless monitoring system. To achieve this the membrane was employed to a printed circuit board (PCB) for a chip level packaging. The degree of functionality was carried out by co-polymerizing 3, 4-ethylenedioxythiphene (EDOT) and 3-thiopheneethanol (3-TE) under various monomer ratio (EDOT:3-TE), where the EDOT provides high conductivity and the 3-TE provides the -OH functional groups to be cross-linked with p-maleimidophenylisocyanate for the antibody attachment. Two-point probe measurement was performed in order to quantify the sensitivity of the resistive response upon exposure to analyte at systematically varied bacterial concentration. The verification of the functional co-polymer thin films were carried out by Fourier transform infrared (FTIR), UV-visible, X-ray photoelectron spectroscopies (XPS), and by scanning electron microscopy (SEM). And, a higher bonding of E. coli with higher functional groups on the sensor was revealed from Green-light, and SEM. Real time detection and monitoring of E. coli has been measured by Two-point probe in this biosensor configuration.

26	Investigation of Quartz Crystal Microbalance (QCM) for Determination of Viability of Hepatitis A Assay Eluate	Torosian, Stephen ORA/WEAC , Bandremer, Aaron Commissioners Fellow ORA/WEAC; Goktas, Hilal ORISE Fellow ORA/WEAC	The critical measure of biological regulatory assays is that they are capable of being utilized to protect the public from exposure to pathogens. For bacterial pathogens an increase in cell number is generally accepted to infer viability, thus the ability to cause disease. For viral pathogens a measurable increase in particle number gives incomplete information about the ability to confer disease to a susceptible individual. The proportion of viral replicates incapable of producing disease varies depending on the virus. Researchers have reported that a large proportion of viral replicates may be incapable of producing infectivity in a susceptible host. While PCR and RT-PCR can be used to show an increase in amount of viral nucleic acid and infer viral genome number, it provides no information about infectivity. To date, the only way to assess that ability in vitro is to perform a plaque assay which typically requires days to visualize/assess. For some viruses such as Hepatitis A Virus (HAV) strain HM175 plaque assay may be extensively prolonged or not even possible. We are investigating the ability of Quartz Crystal Microbalance (QCM) techniques to rapidly assess the viability of the non-pathogenic HAV virusHM175 from eluate(s) of the BAM HAV method. The quartz crystals employed in QCM have a piezoelectric character which allows measurement of nano changes in mass which occur on the surface of the crystals. Researchers have used QCM to specifically trap viruses but QCM has not been used to verify the growth of viral numbers within a live cell or cell population. We are employing QCM to measure frequency changes in minutes when a cell line, Fetal Rhesus Kidney (frhk) cells are inoculated with viral assay extract spiked with HAV. Frequency measurement changes of a spiked sample can be compared to frequency measurements from frhk cells which have not been spiked with HAV. When mass changes of the spiked sample versus the unspiked sample occur, viral growth (viability) is occurring. This tool can be utilized to quickly verify the potential infectivity of a regulatory viral assay isolate. Ongoing efforts are exploring additional species of viral viability targets.
27	Developing Field Screening Methods Using Surface-Enhanced Raman Spectroscopy (SERS) Sensors	Shareef, Abdur-Rafay, Office of Regulatory Affairs (ORA), Winchester Engineering and Analytical Center (WEAC), Winchester, MA 01890; Pogue, Laura, Center for Drug Evaluation and Research (CDER), Division of Pharmaceutical Analysis (DPA), St. Louis, MO 63101 ; Yakes, Betsy Jean, Center for Food Safety and Applied Nutrition (CFSAN), Office of Regulator Science (ORS), College Park, MD 20740	Currently the FDA's analytical repertoire is concentrated in laboratories; whereby inspectors collect and send samples for analysis. Synergistically merging advances in risk based triage and field screening would enable the FDA to proactively monitor the United States food and drug supply. Traditionally, Raman spectroscopy was overlooked for other spectroscopic methods due to lack of sensitivity. However, advances in plasmonics and lithography have yielded uniform, low-cost gold nanoparticle sensors enabling rapid, sensitive analyte detection using surface-enhanced Raman spectroscopy (SERS). We are developing methods enabling non-experts to quickly and efficiently assay foods, excipients, and drugs for contaminants in the field. Elegant and detailed analyses may be accomplished in dedicated laboratories; however, for field screening, sample throughput and simplicity are paramount. Our initial method development is focusing on milk, milk products, lactose and bulk protein products in order to detect the presence of compounds potentially used in economic adulteration; whereby, the protein content, as determined via nitrogen amount, is artificially enhanced by the addition of nitrogen rich, low molecular weight compound(s). Recent events, including the use of melamine for adulteration of Chinese infant formula and milk in 2008, highlight the need for screening a multitude of consumer products. Continued vigilance is necessary due to the international community relying on the Kjeldahl method for determining nitrogen concentration, and then correlating percent nitrogen to protein content. Our initial focus described above is the first application; we envision building SERS sensor methods pragmatically. Future method development activities will broaden to include additional FDA regulated products. Nitrogen containing, small molecules are ubiquitous and can be found in/as pesticides, drugs, and commodity chemicals. Furthermore, SERS is not limited to nitrogen compounds and products, and we envision using this method for multiple future applications.

30	Targeting Triple Negative Breast Cancer in African-American Women	Regis, Kenny, Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Jaldin, M, Trinity Washington Univ. ; Oluwasanmi, Olusayo, Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ.; Duttargi, Anju, Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Mahajan, Akanksha, Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Sugita, Bruna, Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Boca, Simina, ICBI, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Sheahan, Laura, ICBI, Lombardi Comprehensive Cancer Center, Georgetown Univ. ; Gusev, Yuriy, ICBI, Lombardi Comprehensive Cancer Center, Georgetown Univ.; Madhavan, Subha, ICBI, Lombardi Comprehensive Cancer Center, Georgetown Univ., **Cavalli, Luciane, (presenting author), Dept. of Oncology, Lombardi Comprehensive Cancer Center, Georgetown Univ.**	The incidence and outcome of triple negative breast cancer (TNBC) has been shown to vary among the different ethnic and racial groups. Patients from African-American (AA) population present with an increased incidence and shorter survival rate of TNBC when compared to Caucasian women. Social-economic factors alone cannot explain this observed disparity. Therefore, the main objective of our study is to identify the biological factors in TNBC of AA patients that may contribute to their high incidence and mortality rates. TNBC cases from 26 and 28 patients from AA and Caucasian women, respectively, were obtained with clinical annotated data from the Washington DC area. Non-TNBC cases from the same groups were obtained as controls. All the cases were analyzed for DNA copy number (array-CGH-Agilent Platform) and miRNA expression (Nanostring System) alterations. The miRNA data was directly integrated with the array-CGH data from the same cases. Combinatorial target predicted algorithms in conjunction with functional and pathway annotation enrichment systems were performed to identify predicted target functions. A distinct DNA copy number profile was observed between TNBC of AA and Caucasian cases: the cytobands preferentially involved in the AA-TNBC cases were 7p22.3-22.1, 12p13.33-p11.1, 17q25.3 and 17p13.3-p11.2. Common cytobands in both groups were 1q21.1-q44, 8q22.1-q24.3, 16p13.33-p11.1 and 20q11.2-q13.12. MiRNA profiling revealed 209 miRNAs significant differentially expressed between the groups. Unsupervised hierarchical clustering analysis separated the cases by ethnicity (with the exception of 6 cases). Among the miRNAs observed with higher and lower expression levels in the AA cases were miR150-5p, miR4286, miR29b3p and miR1283, miR1253, miR378e, respectively. Ingenuity pathway analysis identified molecular and cellular functions mostly related to cellular development, proliferation and movement and cell death and survival. In conclusion, a distinct DNA copy number and miRNA profile was observed in the AA-TNBC cases when compared to the Caucasians cases of our study. These initial findings will provide the basis for the functional analysis of the identified molecular markers and their potential prognostic and therapeutic impact for this group, which can ultimately lead to the reduction of their observed cancer disparity.
31	Knowledge Regarding Antidepressant Medication among Depressed Latino Patients in Primary Care	Green, Bonnie L., Psychiatry, Georgetown University School of Medicine, Washington, DC; presenting author Kaltman, Stacey, Psychiatry, Georgetown University School of Medicine, Washington, DC; Watson, Maria Rosa, Primary Care Coalition of Montgomery County, Silver Spring, MD; Serrano, Adriano, Psychiatry, Georgetown University School of Medicine, Washington, DC; Talisman, Nicolas, Psychiatry, Georgetown University School of Medicine, Washington, DC; Kirkpatrick, Laura, Psychiatry, Georgetown University School of Medicine, Washington, DC; Campoli, Marcela, Primary Care Coalition of Montgomery County, Silver Spring, MD	Underserved ethnic groups experience significant mental health disparities in services, quality of care, and outcomes. Latinos prefer treatment in primary care, and psychotherapy to medications for depression. This study used an existing sub-sample of depressed Latino immigrant primary care patients who were taking antidepressants (psychiatric medications), drawn from a larger naturalistic treatment study in two safety-net clinics. Patients were queried about their knowledge, attitudes, and preferred ways to receive education about antidepressants. Providers described challenges in prescribing these medications. Individual interviews with 28 patients, and focus groups with 12 patients and 12 providers, generated qualitative data to address these issues. Findings showed that patients and providers have similar observations about challenges in prescribing and taking antidepressants and about fostering understanding about medication action, how to take medications, side effects, and risks/benefits. However, patients do not always hear or understand the messages that providers are attempting to convey, and providers do not always have the time and resources to convey those messages clearly and to follow up. Patients and providers have excellent suggestions for how best to convey information about antidepressants (psychiatric medications) to patients so there is more clarity and less misunderstanding.

32	Literature mining, curation and standardization to develop evidence for biomarkers that predict response to cancer therapy	Rao Shruti, Innovation Center for Biomedical Informatics, Georgetown University (presenting author); Riazi Shahla, Innovation Center for Biomedical Informatics, Georgetown University; Boca Simina, Innovation Center for Biomedical Informatics, Georgetown University; Singh Varun , Innovation Center for Biomedical Informatics, Georgetown University; Harris Michael, Innovation Center for Biomedical Informatics, Georgetown University; McGarvey Peter, Innovation Center for Biomedical Informatics, Georgetown University; Pishvaian Michael J., Department of Hematology/Oncology, Lombardi Comprehensive Cancer Center, Georgetown University; Brody Jonathan, Department of Surgery, Thomas Jefferson University; Madhavan Subha, Innovation Center for Biomedical Informatics, Georgetown University	Background Cancer biomarkers can improve early disease detection and provide guidance on choosing appropriate individualized therapies. Tumor boards are faced with challenges in making therapy decisions based on empirical evidence. Our goal was to extract, standardize, and organize molecular information and treatment options from predictive biomarker related publications that can ultimately be used to understand clinical utility of these biomarkers. Methods We used PubTator, a web based text mining tool, to extract relevant PubMed articles about chemopredictive biomarkers and associated therapies. Each article was organized into six broad categories: 1) disease 2) biomarker 3) therapy 4) outcome 5) study information 6) evidence curation. Data was manually curated and standardized within each of these categories to determine the predictive effect of biomarkers on therapeutic outcomes. We then identified study types and assigned evidence levels ranging from I-V to these articles. Results We manually curated 70 PubMed articles on RRM1 and 43 PubMed articles for TUBB3 as a predictive cancer biomarker. Our results show that, in general, low expression levels of RRM1 and TUBB3 are associated with benefit of gemcitabine and taxane based therapies respectively. However, evidence levels supporting this association vary for different cancer types. For lung cancer, more level I and II studies show benefit of low RRM1 expression on gemcitabine-based therapies whereas for gastro intestinal cancers, there is only level III evidence demonstrating benefit. Curation of other predictive biomarkers is ongoing. Conclusion We discovered that peer reviewed studies that involved predictive biomarkers had: 1) a diversity of methods used; 2) at times, an inconsistency in conclusions; and 3) clinical information based on the tumor type (e.g., lung vs pancreas). The organization and analysis of dispersed public data for retrospective biomarker analysis and other associated metadata enables researchers to readily generate hypotheses for new clinical trials and to explore the use of published markers to stratify patients upfront for ‘best-fit’ therapies.
33	Health Literacy and Information Regarding Medical Products Supporting Aging in Place	Saunders, Pamela, A.; Georgetown University School of Medicine	With the rapid aging of our populations we wanted to understand how older adults gain and process information regarding medical products that allow them to age in place. In order to address these issues, we explored the kinds of medical products (a term that encompasses “medical devices”) people used and the information sources they used to obtain information about medical products to support aging in place. We used a mixed methods approach (focus groups and survey instrument) to understand how individuals obtain information about medical products. We conducted 5 focus groups and collected over 200 surveys. We discovered the most reported medical products were: glasses, bath mats, and blood pressure cuffs. The most reported individual sources of information were: physicians, family, and friends. The most reported media sources were the Internet, newspaper, television, and radio. The most reported websites were: AARP.org, Mayoclinic.com, WebMD.com and TV shows were: The Doctors, Oprah, and Dr. Oz. We found that health literacy makes a limited difference in types of medical products used; but some differences in individual information sources as well as other information sources used. Further we found very few differences in levels of trust as stratified by health literacy. We plan to continue this research by working with older adults who are aging in place to learn about their needs in terms of information about medical products and well as technological advancements.

34	Challenges to and Successful Strategies for Patient Engagement in Research	**Ellis, Lauren, Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins Berman Institute of Bioethics;** Kass, Nancy, Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins Berman Institute of Bioethics	Patient engagement in research refers to researchers involving patients in research in ways other than as subjects of research and includes activities falling anywhere on a spectrum from low levels of engagement such as single consultations with patients to active patient-researcher collaborations or even patient-led research. Despite increasing support for patient engagement in research, guidance on how to engage patients is limited. The aim of this study was to describe challenges to and successful strategies for patient engagement. Qualitative interviews were conducted with 19 investigators of projects funded by the Patient-Centered Outcomes Research Institute (PCORI) and with 33 patients engaged in 18 of the same 19 projects. Informants reported experiencing logistical and substantive challenges. Logistical challenges referred to challenges in planning engagement, including extra time and effort, difficulty working with investigators' institutions and with institutional review boards, and difficulty having and scheduling meetings. Substantive challenges included challenges to selecting, orienting, and interacting with patients and to incorporating patient feedback. Successful techniques included using existing resources, communicating goals, providing patient education, and treating patients respectfully. These findings suggest actions for consideration that are relevant to policymakers, funders, institutions, and researchers. Modifications to policies, the development of programs and researcher networks, and the provision of resources and training are suggested. Future research should evaluate the effectiveness of such actions in strengthening engagement. As opportunities for engaging patient in research continue to grow, bolstering the infrastructure for patient engagement must remain a priority.
35	Development of regulatory approaches to optimizing safe use: the case of nursing home opioids	**Kevin M. Fain, JD, MPH**, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, W6508, Baltimore, MD 21205 (kfain1@jhu.edu) (Presenting Author); Carlos Castillo-Salgado, MD, JD, MPH, DrPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, E6136, Baltimore, MD 21205 (ccastil3@jhu.edu); G. Caleb Alexander, MD, MS, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, W6035, Baltimore, MD 21205 (galexan9@jhmi.edu).	Purpose: Due to its risks, the U.S. Food and Drug Administration has warned that transdermal fentanyl be limited to individuals with prior opioid use and persistent pain. These risks are particularly acute in elderly patients. Our objective was to quantify prevalence of transdermal fentanyl prescribing in elderly nursing home residents without prior opioid use or persistent pain and the association of individual and facility traits with opioid-naïve prescribing. Design: Cross-sectional study. Setting: Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims. Participants: From a cross-section of all long-stay US nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified individuals (≥65 years old) who initiated transdermal fentanyl, excluding those with dementia, severe cognitive impairment, cancer or receipt of hospice care. Measurements: We used Medicare Part D to select beneficiaries initiating transdermal fentanyl in 2008 and examined whether they were "opioid-naïve," defined as no opioid prescriptions during the previous 60 days. We obtained resident and facility characteristics from MDS and OSCAR records and defined persistent pain as moderate-to-severe, daily pain on consecutive MDS assessments at least 90 days apart. We estimated associations of patient and facility attributes and opioid-naïve fentanyl initiation using multilevel mixed effects logistic regression analyses. Results: Among 17,052 residents who initiated transdermal fentanyl, 6,190 (36.3%) were opioid-naïve and 15,659 (91.8%) did not have persistent pain. In the regression analysis with adjustments, residents who were older (≥95 years old, odds ratio (OR)= 1.69, 95% confidence interval (CI) = 1.46-1.95) or more cognitively impaired (moderate-to-severe cognitive impairment, OR=1.99, 95% CI = 1.73-2.29) were more likely to initiate transdermal fentanyl without prior opioid use. Conclusion: Most nursing home residents initiating transdermal fentanyl did not have persistent pain and many were opioid-naïve. This inappropriate use was even more likely for vulnerable subpopulations such as the cognitively impaired. Implications: FDA should consider actions to ensure more appropriate transdermal fentanyl prescribing in nursing homes, including specific guidance and risk communication to nursing homes and additional steps for institutional settings in the long-acting opioid Risk Evaluation and Mitigation Strategy (REMS).

36	Developing Common Data Elements for Outcomes for Selected Eye Conditions: Case Example with MIGS Trials	**LE, JIMMY**; Viswanathan, Shilpa; Dickersin, Kay; Li, Tianjing Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore MD	**Background**: Harmonizing clinical trial outcomes across trials is desirable to facilitate cross-study comparisons and streamlining regulatory and public health decision-making. We sought to review outcomes used in practice, explore patientperspectives, and propose a framework for selecting outcomes. Working in collaboration with the Center for Devices and Radiological Health at FDA, we focus on minimally invasive glaucoma surgery (MIGS) device trials as a case example. **Purpose**: To summarize MIGS-device trials outcomes registered on ClinicalTrials.gov and discuss implications for the next step in our project, seeking patients' views on important efficacy and safety outcomes. **Methods**: We worked with an informationist to search for all studies registered on ClinicalTrials.gov that included MIGS device as the intervention and glaucoma and/or cataract as the condition on February 20, 2015. Two authors independently extracted data from eligible records, including population, intervention/comparison, and specification of outcomes (i.e. domain, measurement, time-points, metric and method of aggregations). No results data were abstracted. **Results/Accomplishments to date**: We found 51 registered MIGS trials: 44/51 were industry-funded, 35/51 were reported to be Phase III- or IV-trials; 32/51 were reported to be studying non-FDA-regulated interventions; and 30/51 trials were reported as randomized. All 51 trials designated glaucoma as at least one of the conditions of interest, though three also included cataracts. We identified 128 unique outcomes, covering 4 main outcome domains: intraocular pressure (IOP) (78/128), ocular medication use (16/128), visual acuity (4/128), and adverse events (17/128). Fewer than half of the domains (50/128) can be classified as patient-important, defined as outcomes of direct value to patients. Among IOP-based outcomes, 45/78 were registered as a primary outcome for the trial. **Conclusions and Implications**: IOP was the most frequent outcome; however, this is an interim outcome, perhaps not generally considered patientimportant. Our next step is to engage patients and solicit their input on the relative importance of outcomes.

37	Uremic Toxins Inhibit Organic Anion-Transporting Polypeptide 1B1 (OATP1B1) and Organic Anion-Transporting Polypeptide 1B3 (OATP1B3) at Clinically Relevant Concentrations	**Hsueh, Chia-Hsiang**,University of California, San Francisco; Yoshida, Kenta, US Food and Drug Administration; Huang, Shiew-Mei, US Food and Drug Administration; Zhang, Lei, US Food and Drug Administration; Meyer, Timothy, Stanford University; Sirich, Tammy, Stanford University; Giacomini, Kathy, University of California, San Francisco	Purpose of research FDA recommends pharmacokinetic studies on patients with renal impairment even for drugs whose hepatic clearance are dominant. Accumulating evidence to-date suggests that renal impairment can also lead to alterations in hepatic clearance by affecting transport. Organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3) are two major hepatic transporters and play important roles in drug elimination. We investigated whether uremic toxins, which accumulate in renal impairment, will inhibit the activities of these two transporters. Method and findings Estrone sulfate and 6-carboxyfluorescein diacetate were used as the model substrates for OATP1B1 and OATP1B3 respectively. Inhibition of uptake was evaluated by co-incubation of the model substrate and different uremic toxins. We found at around 100x free uremic concentration, creatinine, indoxyl sulfate, and p-cresyl sulfate significantly inhibited OPTP1B1 by 38%, 53%, and 31%. Homocysteine and indoxyl sulfate inhibited OATP1B3 by 79%, and 33%. The IC50 of indoxyl sulfate was 2232±61uM for OATP1B1 and 1077±67uM for OATP1B3. Homocysteine inhibited OATP1B3 at the IC50 of 1108±53uM. Those values are clinical relevant. Moreover a cocktail of indoxyl sulfate, homocysteine, and p-cresyl sulfate further diminished the uptake of estradiol 17-(β-D-blucuronide) via OATP1B1 and OATP1B3 than a single uremic toxin did. Accomplishments to date and Conclusions We have identified several uremic toxins that inhibit OATP1B1 and OATP1B3. Notably, indoxyl suflate is a mutual inhibitor of OATP1B1 and OATP1B3 while homocysteine is a potent inhibitor of OATP1B3. We further showed a cocktail of uremic toxins had greater inhibitory effect. This suggests the accumulated uremic toxins in renal impairment might collectively inhibit the activity of OATP1B1/1B3 and lead to altered pharmacokinetics for certain drugs as observed clinically. Implications or impact of the work. Some uremic toxins are inhibitors for OATP1B1 and/or OATP1B3. Especially indoxyl sulfate is a mutual and potent inhibitor for OATP1B1 and OATP1B3. These uremic toxins might be potential biomarkers for the activities of transporters and could be integrated into PBPK model to predict the effect of renal impairment on the pharmacokinetics
38	Improving Health Literacy and Cultural Competency of FDA Consumer Materials on Cardiovascular Disease	TRamsey, Lauren (UMD SPH Epidemiology and Biostatistics) Fix, Jonathan (UMD IVSP) Carter-Pokras, Olivia (UMD SPH Epidemiology and Biostatistics) Presenter Name Jonathan Fix	Background: People with serious chronic health conditions such as cardiovascular disease (CVD), and those facing barriers to the traditional healthcare system, often use the internet to obtain health information. However, low health literacy, or the ability to understand and process health information in order to make informed healthy decisions, can act as a barrier to chronic disease management. Objective: Assess the health literacy and cultural competency of Food and Drug Administration (FDA) consumer web pages on CVD. Methods: A grading rubric was developed according to best practices in assessing cultural competency, readability and plain language aspects of written materials, and applied by 2 reviewers to 25 consumer pages on CVD (hypertension, ACE inhibitors, high blood pressure, coronary heart disease, cardiovascular disease). A systematic review of the literature was conducted to identify consumer preferences when seeking information online regarding cardiovascular disease prevention or management. Results: Most of the web pages were cluttered with lots of words and few graphics and white space. The average Flesch Kincaid reading level for the webpages was 10.3. The majority of the web pages did not provide contact information for questions, or mention a particular racial/ethnic group directly or indirectly. Conclusions: These results underscore the need to get consumer input during development of materials intended for dissemination through the Internet. Learning how to communicate public health information through a variety of media to diverse audience is a key component of undergraduate public health education, and communication skills and cultural competency are core competencies for public health professionals.

39	3D-Printed Tissue-Simulating Phantoms for Testing of Biophotonic Imaging Devices	Wang, Jianting FDA; Jang, Hyounguk UMCP, FDA; Ghassemi, Pejhman FDA; Coburn, James FDA; Ramella-Roman, Jessica Florida International Univ.; Chen, Yu UMCP; Pfefer, Joshua FDA	Biophotonic imaging devices are emerging technique as an important clinical tool for minimally-invasive cancer detection, physiological monitoring (e.g., oximetry) and intraoperative tumor identification. Basic 3D printed tissue simulating phantoms have been shown the potential for evaluation of biophotonic imaging systems. There is a need for standardized methods to evaluate HRI device image quality in a quantitative, objective and biologically-realistic manner. Phantom-based test methods can facilitate the regulatory process, preclinical testing in support of device effectiveness. We fabricate phantoms based on a previously acquired fundus camera image of the human retina by mimicking its structure in a 3D matrix and converting into a digital format suitable for printing. We printed phantoms with the retinal vascular network reproduced as ~1.0 mm diameter channels at a range of depths up to ~3 mm. A polymer with biologically realistic optical properties of several commercially available samples was measured by a spectrophotometer. We investigated the potential of phantom-based methods for the evaluation of HRI systems, especially imaging penetration depth, lowest detectable concentration of contrast agent. Our results demonstrated that 3D printed phantoms can be beneficial for assessing biophotonic system performance and have the potential to be a clinically-relevant standardized test method for assessment of medical imaging devices.
40	Fabrication and Vascularization of Tissue Engineering Sleeve Scaffolds	Wang, Martha O. UMCP; Dreher, Maureen L. FDA, Eric M. Brey, Eric M. Illinois Institute of Technology; Fisher, John P. UMCP	The recent proliferation of three dimensional (3D) printing technologies has allowed the exploration of increasing complex designs, and, furthermore, the consideration of 3D printed constructs for biological applications. 3D printed scaffolds that are designed to include a space to house additional materials are referred to as sleeve scaffolds. Sleeve scaffolds have many advantageous properties in bone tissue engineering including mechanical support containing bioactive materials such as hydrogel encapsulated precultured stem cells. We demonstrate here the design, fabrication and vascularization of 3D printed sleeve scaffolds. Our work identifies the range of design specifications using a modular design, predicts host vessel integration through an in silico model and compares the results to an in vivo model. For this work we designed, fabricated, and evaluated polymer scaffolds using an absorbable poly(propylene fumarate) based resin. Our work highlights the potential for these tools to be combined as a consistent methodology for the evaluation of porous 3D printed constructs for regenerative medicine.
41	Microsystems for Characterization, Prevention, Sensing and Treatment of Bacterial Biofilms	Subramanian, Sowmya UMCP; Gerasoupolos, Konstantinos UMCP; Meyer, Mariana UMCP; Kim, Young Wook UMCP; Bentley, William UMCP; Ghodssi, Reza UMCP	In this work, we summarize the development of compact microsystems for the characterization, prevention, sensing, and treatment of bacterial biofilms. We present in-vitro platforms for biofilm characterization, in-vivo systems for biofilm sensing and treatment and new methods for biofilm prevention. Non-invasive characterization for the investigation of the fundamental mechanisms of biofilm formation and growth under a variety of conditions was achieved using simple opto-electronic microfluidic systems that can not only provide parallel operation, but also a tightly controllable microenvironment. Furthermore, the sensing and treatment of biofilms at early stages of growth is critical in the management of biofilm associated infectious diseases. A surface acoustic wave (SAW) micro-sensor, with integrated electrodes for treatment using the bioelectric effect was developed for the early detection and effective treatment of biofilms. We also suggest new strategies to prevent biofilm adhesion through the use of modified surfaces and biofilm formation using small molecule inhibitors that prevent critical pathways necessary for biofilm growth.

42	Patient Engagement in Research as Co-Developers of Trials	Mullins, C. Daniel UMB; Connor, Jason Berry Consultants, LLC.; Broglio, Kristine Berry Consultants LLC	We designed and executed the use of Bayesian approaches and applications of the ALLHAT study that allow simulation of patients choosing the arm that they prefer and assigning a higher probability of random assignment to that arm. The results show that there is little change in the hazard ratios (HRs) of events based upon these simulated results as compared to the actual ALLHAT results. Although not statistically significant, the sub-analysis based upon racial subgroups did show a slight impact on the point estimate of the HRs for the entire population, which merits further exploration related to heterogeneity of treatment effect. The implications are that future regulatory trials that allow for patients to express their preferences for a particular arm yet preserve random assignment may result in valid biostatistical approaches that are more patient centered. Further exploration of this concept could aid patient-centered drug development.
43	NTCP Pharmacophore and Lack of Association between DILI and NTCP Inhibition	Dong, Zhongqi UMB ; Ekins, Sean Collaborations Pharmaceuticals ; Polli, James UMB	The human sodium taurocholate cotransporting polypeptide (NTCP) is a hepatic bile acid transporter. Inhibition of NTCP uptake may potentially also prevent hepatitis B virus (HBV) infection. The first objective was to develop a quantitative pharmacophore for NTCP inhibition. Recent studies showed that hepatotoxic drugs could inhibit bile acid uptake into hepatocytes, without inhibiting canalicular efflux, and cause bile acid elevation in plasma. Hence, a second objective was to examine whether NTCP inhibition is associated with drug induced liver injury (DILI). Twenty-seven drugs from our previous study were used as the training set to develop a quantitative pharmacophore. From secondary screening from a drug database, six retrieved drugs and three drugs not retrieved by the model were tested for NTCP inhibition. Tertiary screening involved drugs known to cause DILI and not cause DILI. Overall, ninety-four drugs were assessed for hepatotoxicity and were assessed relative to NTCP inhibition. The quantitative pharmacophore possessed one hydrogen bond acceptor, one hydrogen bond donor, a hydrophobic feature, and excluded volumes. From 94 drugs, NTCP inhibitors and non-inhibitors were approximately equally distributed across the drugs of most DILI concern, less DILI concern, and no DILI concern, indicating no relationship between NTCP inhibition and DILI risk. Hence, an approach to treat HBV via NTCP inhibition is not expected to be associated with DILI.
44	Mechanistic insight into metformin-mediated repression of BSEP	Garzel, Brandy, UMB(Presenting); Yang, Hui, UMB; Heyward, Scott, Bioreclamation IVT; Zhang, Lei, FDA; Huang, Shiew-Mei, FDA; Polli, James E., UMB; Wang, Hongbing, UMB	**Purpose:** Drug-induced cholestatic liver injury is a toxic side effect for a number of FDA-approved drugs, though its cause is still not completely understood. Current research regarding drug-induced cholestasis primarily focuses on the inhibitory capacity of drugs for the bile salt export pump (BSEP) while often overlooking the importance of drug-induced gene repression. Metformin, a widely used type 2 diabetic drug, has been linked to cholestatic liver injury in a number of case reports; however metformin has no inhibitory effect on BSEP activity. **Methods:** In this report, human primary hepatocytes were used to assess metformin-mediated alteration of BSEP gene expression and function. The underlying mechanisms were further analyzed in cell expressing constitutively active(CA)- or dominant negative(DN)-adenosine monophosphate-activated protein kinase (AMPK), farnesoid x receptor (FXR), liver receptor homolog-1 (LRH-1) or nuclear factor (erythroid-derived-2)-like 2 (NRF2). **Results:** Our data indicate that metformin can potently repress BSEP expression in human primary hepatocytes in a concentration-dependent manner. Interestingly, although metformin did not directly interact with BSEP, metformin-mediated BSEP repression resulted in decreased efflux of taurocholate in human primary hepatocytes. We have found that increased activity of AMPK, whether chemically or with adenoviral infection, leads to decreased BSEP gene expression. On the other hand, metformin appears to disrupt chemically activated but not basal activity of FXR in cell-based luciferase assays. **Conclusions:** Overall, these results indicate that BSEP function can be altered through gene repression without direct inhibition of BSEP activity, providing important information regarding the development of cholestatic liver injury, particularly under chronic drug exposure. Our results also indicate AMPK activation plays a role in drug-induced BSEP repression. This information could be useful in screening for cholestatic potential of new drugs.

45	Inkjet-printed fluidic paper SERS devices for chemical and biological analytics	Yu, Wei W. UMCP; Hoppmann, Eric P. UMCP; White, Ian UMCP	As a bio/chemical sensing technique, surface enhanced Raman spectroscopy (SERS) offers sensitivity comparable to that of fluorescence detection while providing highly specific information about the analyte. The high sensitivity of SERS detection results from the localized plasmons generated at the surface of noble metal nanostructures upon excitation by resonant electric fields at optical frequencies. Although single molecule identification with SERS was demonstrated over a decade ago, today a need exists to develop practical solutions for point-of-sample and point-of-care SERS systems. Recently, we demonstrated the fabrication of SERS substrates by inkjet printing silver and gold nanostructures onto paper. Using a low-cost commercial inkjet printer, we printed silver nanoparticles with micro-scale precision to form SERS-active biosensors. Using these devices, we have been able to achieve detection limits comparable to conventional nanofabricated substrates. Furthermore, we leverage the fluidic properties of paper to enhance the performance of the SERS devices while also enabling unprecedented ease of use. Paper dipsticks concentrate a relatively large sample volume into a small SERS-active detection region at the tip. Likewise, paper swabs collect samples from a large surface area and concentrate the collected molecules into a SERS sensor on the paper. In addition, the inherent chromatographic properties of paper enable sample cleanup and analyte separation to improve detection in complex real-world samples.
46	Novel Noninvasive In Situ Post-Production Quantification of Aggregates in Biopharmaceutical Drugs. The Case of Insulin	Taraban, Marc B. UMB; Truong, Huy UMB; Feng, Yue UMB; Yu, Y. Bruce UMB	Problems of quality control of the biopharmaceuticals in aqueous solutions become more and more pressing. At present, their degrading safety due to the aggregation of the active factor could be monitored only by `invasive' techniques (SEC, AUC, etc.). These techniques require the opening of the container and render the drug unusable even if it is not considered degraded. Here, we used human insulin solutions to demonstrate that transverse relaxation rate of water could serve as a sensitive and reliable indicator which allows to detect and quantify aggregation. Moreover, this water property could be measured by inexpensive wide-bore bench-top NMR instruments without opening the drug container, thus saving it for further use.
47	Absolute Quantification Method for Protein Concentration	LI, MINGDONG, UMD; Tan, Jiaojie, UMD ; Tarlov, Michael, NIST; Zachariah, Michael, UMD	Several traditional methods are available for protein quantification; however, these methods ether lack accuracy or are time-consuming and laborious for large proteins. Here, a fast and accurate assay to determine the absolute concentration of proteins [1] is described based on direct measurement and statistical analysis of droplet entrapped oligomer formation in electrospray [2, 3]. The charge residue mechanism indicates the existence of a droplet entrapped nonspecific aggregation effect, i.e., two intrinsic monomers randomly entrapped in a droplet are observed as a dimer in the final analytical distribution after the droplet drying. Here we demonstrate the approach using electrospray differential mobility analysis (ES-DMA), which can distinguish monomers and dimers from higher order oligomers. A key feature of the method is that it allows determination of the absolute number concentration of proteins eliminating the need for protein-specific calibration. The method was demonstrated by measuring the concentration of a NIST Standard Reference Material 927e (bovine serum albumin), a high-purity immunoglobulin G 1κ, and a formulated Rituximab [1]. The method may be applied to any electrospray source, regardless of diagnostic tool (e.g., MS or ion mobility, etc.), provided the electrospray is operated in a droplet-fission mode.

48	Addressing Racial/Ethnic Differences in ADHD Diagnosis and Treatment Among Medicaid-insured Youth in California	Pennap, Dinci MPH; 1 Burcu, Mehmet MS; 1 Safer, Daniel MD; 2 Zito, Julie PhD1, 3 1Pharmaceutical Health Services Department, University of Maryland, Baltimore MD 2Departments of Psychiatry and Pediatrics, Johns Hopkins Medical Institutes, Baltimore MD 3Department of Psychiatry, School of Medicine, University of Maryland, Baltimore MD	**Background**: Population-based studies of Medicaid administrative claims data document mental health service utilization in youth on the order of 50-60% lower among minority populations. Residential locale can be measured in terms of the degree to which two or more racial groups live separately from one another in a geographic area. Residential segregation (RS) may imply differences in access and availability of services as well as cultural preferences that limit use of medical care. **Objective**: To assess whether residential segregation of Hispanic youth contributes to reduced mental health treatment services. **Methods**: A cross-sectional design was applied to the 2009 claims data of continuously enrolled youth (2-17 years), representing 83.7% of the state's Medicaid youth population (N = 2,221,010). As a proxy for RS, regional Hispanic composition (RHC) was measured as a proportion of the Hispanic population in the Medicaid enrollee's zip code of residence and characterized as < 25%, 25% - 50%, and >50%. Bivariate analyses were conducted to assess: 1) percent prevalence of ADHD diagnosis; and 2) percent of stimulant use among ADHD diagnosed youth. Multivariable analyses were used to examine Hispanic to White differences in ADHD diagnosis and stimulant use across levels of Hispanic residential segregation, adjusting for study covariates. **Results**: Continuously-enrolled youth were predominately Hispanic (63.7%), less than 10 years old (54.2%), and eligible for Medicaid based on low family income (89.9%). Among ADHD diagnosed youth, 59.8% received at least 1 stimulant dispensing. Hispanic youth residing in highly segregated areas (>50% Hispanic composition) were; 1) more likely to have median household income <$50,000; 2) 66% less likely to receive an ADHD diagnosis; and 3) 35% less likely to receive a stimulant dispensing following an ADHD diagnosis compared to White youth. **Conclusion**: Hispanic to White differences in treatment service utilization intensified with increasing levels of regional Hispanic composition. Among ADHD diagnosed youth, Hispanic to White differences in stimulant use were substantially smaller than the Hispanic to White differences in ADHD diagnosis. Residential segregation research should be further pursued to corroborate these findings in other state Medicaid programs and among privately insured youth so as to expand the framework for health disparity research and policy planning for child mental health services.
49	Perceptions of Patient Prescriber Agreements: Preliminary Results from a Focus Group Study	Albrecht, Jennifer PhD, UMB; Bilal Khokar, Bilal MS, UMB; Pradel, Francoise PhD, UMB; Michelle Campbell MS, UMB; Palmer, Jacqueline PharmD, UMB; Palumbo, Frank MS, PhD, JD, UMB; Ilene Zuckerman PharmD, PhD, UMB	Use of patient provider agreements (PPAs) is increasing, yet there is limited evidence on the effectiveness of PPAs to prevent prescription opioid misuse and diversion, and few guidelines for providers. We conducted eight focus groups to understand patient and prescriber perceptions of PPAs. We recruited 40 patients who had been asked to sign a PPA, and 40 prescribers who had administered at least one PPA. We developed topic guides for the two groups based on prior literature. Focus groups were audio-recorded and transcribed verbatim. Two investigators independently performed the content analysis of the transcripts and reached consensus on recurring themes. PPA use varied according to physician specialty. General practitioners used PPAs the least but reported increasing pressure from liability insurers to use them. Many patients reported signing a PPA in the emergency room of a hospital. We identified several themes concerning the administration, content, effectiveness, and utility of PPAs that highlight areas of research to improve PPAs. Prescribers and patients reported a lack of understanding among patients concerning the purpose and content of the PPA. Prescribers questioned the legal status of the PPA, while patients believed that the PPA was a legal document intended to protect prescribers. Patients and prescribers valued PPA content items differently, although both groups agreed that signing a PPA would not prevent opioid misuse.