HITS: Harnessing a Collaborative Training Network to Create Case Studies that Integrate High-Throughput, Complex Datasets into Curricula

Sabrina D. Robertson1, Andrea Bixler2, Melissa R. Eslinger3, Monica M. Gaudier-Diaz1, Adam J. Kleinschmit4, Pat Marsteller5, Kate K. O’Toole5, Usha Sankar6 and Carlos C. Goller7*

1Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States, 2Department of Science and Mathematics, Clarke University, Dubuque, IA, United States, 3Department of Chemistry and Life Science, United States Military Academy, West Point, NY, United States, 4Department of Natural and Applied Sciences, University of Dubuque, Dubuque, IA, United States, 5Department of Biology, Emory University, Atlanta, GA, United States, 6Department of Biological Sciences, Fordham University, Bronx, NY, United States, 7Department of Biological Sciences and Biotechnology Program, North Carolina State University, Bronx, NY, United States

As educators and researchers, we often enjoy enlivening classroom discussions by including examples of cutting-edge high-throughput (HT) technologies that propelled scientific discovery and created repositories of new information. We also call for the use of evidence-based teaching practices to engage students in ways that promote equity and learning. The complex datasets produced by HT approaches can open the doors to discovery of novel genes, drugs, and regulatory networks, so students need experience with the effective design, implementation, and analysis of HT research. Nevertheless, we miss opportunities to contextualize, define, and explain the potential and limitations of HT methods. One evidence-based approach is to engage students in realistic HT case studies. HT cases immerse students with messy data, asking them to critically consider data analysis, experimental design, ethical implications, and HT technologies. The NSF HITS (High-throughput Discovery Science and Inquiry-based Case Studies for Today’s Students) Research Coordination Network in Undergraduate Biology Education seeks to improve student quantitative skills and participation in HT discovery. Researchers and instructors in the network learn about case pedagogy, HT technologies, publicly available datasets, and computational tools. Leveraging this training and interdisciplinary teamwork, HITS participants then create and implement HT cases. Our initial case collection has been used in >15 different courses at a variety of institutions engaging >600 students in HT discovery. We share here our rationale for engaging students in HT science, our HT cases, and network model to encourage other life science educators to join us and further develop and integrate HT complex datasets into curricula.

Keywords: high-throughput, collaborative network, data analyses, quantitative skills, pedagogical case studies
INTRODUCTION—A CALL TO INTEGRATE HIGH-THROUGHPUT DISCOVERY SCIENCE INTO CURRICULA

High-throughput (HT) approaches have become critical for contemporary scientific discovery. HT research often leverages the power of automation and miniaturization to make large-scale experimentation feasible and promote discovery. Advances in sequencing (McCombie et al., 2019), drug discovery (da Silva Rocha et al., 2019; Farha and Brown, 2019; Vamathevan et al., 2019; Zhu, 2020), imaging (Pegoraro and Misteli, 2017), proteomics (Tyers and Mann, 2003), machine learning and genome editing are transforming the way scientists perform research. HT approaches allow researchers to conduct multiple chemical, genetic, and phenotypic tests to identify active molecules, conditions, or genes with desired or useful features (Appleton et al., 2017). HT omics have enabled simultaneous examinations of hundreds or thousands of genes, proteins, and metabolites (Judes et al., 2016). Large NIH (Collins, 2010) and NSF initiatives (e.g., BREAD PHENO) also take advantage of HT methodologies (ENCODE, 2004; Regev et al., 2017; Hutter and Zenklusen, 2018; Koroshetz et al., 2018; McDonald et al., 2018). This fast-paced development and diversity of HT approaches necessitates effective training of scientists and engineers (Miller, 2014; Stephens et al., 2015; Batut et al., 2018). To better prepare students for this new HT research world, an understanding of HT approaches and dataset wrangling must be broadly integrated into curricula to empower all students to analyze and discover.

Variations in HT terminology may refer to a discipline (e.g., biology, genetics, bioinformatics), a technique (e.g., screening, sequencing), or a volume of data, but it is the data science and analysis skills that are more essential than ever for STEM students. For students to analyze and appreciate results, a general understanding of how data is validated and processed is required. Yet, undergraduate biology programs have been slow to adopt practices and curricula that enhance such quantitative skills (Feser et al., 2013; Hoffman et al., 2016). Educators have generated a multitude of reports and educational initiatives to fill this void (National Research Council, 2003; Bialek and Botstein, 2004; National Research Council, 2009). Despite the calls to action, there remains a relative dearth of educational resources that engage students with complex, HT datasets aimed at enhancing their quantitative skills (Aikens and Dolan, 2014). In part, this may reflect a lack of sufficient faculty training and a need for professional development and teaching support opportunities (AAAS, 2011). Since the design, execution, and analysis of HT data require fundamental quantitative skills, collectively this provides a ripe opportunity for faculty and students alike to expand these skills. Indeed, these skills align with the first two core competencies outlined by Vision and Change and the BioSkills Guide for revolutionizing undergraduate biology education (AAAS, 2011; Clemons et al., 2020). Successful examples of undergraduate data mining and contribution to research (i.e., Genomics Education Partnership (Lopatto et al., 2014) and Genome Solver programs (Rosenwald et al., 2012) are becoming more common, and this integration of authentic research has a multitude of strongly supported student benefits (Lopatto et al., 2008; Thiry et al., 2011; Jordan et al., 2014; Shaffer et al., 2014).

High-Throughput Discovery Science and Inquiry-Based Case Studies for Today’s Students Network

We created the NSF-funded Research Coordination Network (RCN) known asHigh-throughput Discovery Science & Inquiry-based Case Studies for Today’s Students (HITS), to develop innovative curriculum materials using a case-based approach. RCNs have had a profound scholarly impact (Porter et al., 2012) and continue to generate and disseminate resources that improve research and education. Other RCNs have focused on the development of case studies (NeuroCaseNet, Molecular case Net (Goodsell et al., 2021), OCELOTS), bioinformatics (NIBLSE) or next generation sequencing (GCAT-SEEK). Additional educational initiatives (BEDROCK, ESTEEM, NUMB3R5 COUNT!, EDDIE) aim to increase student quantitative skills in biology but are not focused on case studies or high-throughput discovery science. HITS specifically addresses a unique need for case studies that provide exposure to and practice with manipulating and analyzing high-throughput datasets and understanding HT experimental approaches.

Case-based learning has been adopted and adapted into undergraduate and graduate education (Blosser, 1988; Gallagher et al., 1995; Krynock and Robb, 1996) and has become recognized as a high impact practice that supports Vision and Change core competencies (Lombardi, 2007; Freeman et al., 2014). According to the Vision and Change 2010 report (AAAS, 2011), all students need to develop the ability to apply the process of science, use quantitative reasoning skills, use models and simulations, understand the interdisciplinary nature of scientific investigations, and be able to communicate science well and in collaboration with other disciplines. Students also need to place their science knowledge in a societal context and learn to apply scientific concepts to real world problems. Case-based instructional methods, which include the case study method, problem-based learning, and investigative case-based learning, use realistic narratives to engage students in solving problems, building analytical skills, and working cooperatively in a self-directed way (Herreid, 1994; Torp and Sage, 2002; Duch et al., 2011). The complex nature of case studies leads students to assess problems from a myriad of perspectives and those that emphasize the human dimension of an issue or controversy powerfully demonstrate the relevance of a given topic to students and generate engagement (Yadav et al., 2007). Approaches to writing and adapting case studies have been previously well documented (Herreid, 1997; Herreid, 2018; Prud’homme-Generaux et al., 2018; https://sciencecases.lib.buffalo.edu/teaching/publications/).

Datasets produced by HT approaches contain untold stories about the biological world around us. Providing “scaffolded” cases for students to understand HT methodology, dive into data, and uncover trends promotes quantitative skills, hypothesis development, and the excitement for discovery. The HITS research and educational network provides structure and
support for the development of HT case studies that promote student learning of core HT concepts and competencies. The resulting inquiry-based cases engage students in authentic research and better train future scientists for jobs in modern biology. Recently, our network shared insights on how to adapt HT cases for the classroom (Bixler et al., 2021). The HITS network also includes established non-profit and industry collaborations with researchers, institutes, and companies that produce datasets amenable for exemplary HT case studies. For example, The Allen Institute has worked with HITS to create case studies that use resources on the Allen Cell Explorer and Allen Brain Map websites to engage students in analysis of thousands of microscopy images of engineered cells and real electrophysiology data from human neurons. These datasets and equipment alone encompass several research areas and HT approaches, including sequencing, imaging, and screening. As HITS expands, additional collaborations and projects provide more datasets and resources to explore ways to connect students and courses at different institutions. By partnering researchers, educators, and case study experts to create, implement, and share HT case-based tools, our HITS network improves curricula across the nation and better equips life science students with essential science process skills and complex dataset literacy.

How High-Throughput Discovery Science and Inquiry-Based Case Studies for Today’s Students Cases Are Unique

HT case studies characteristically integrate large quantitative datasets with an engaging biological narrative to directly showcase the real-world relevance of course concepts. The unique features that make HT cases stand out include the combined focus on HT experimental approaches and contemporary techniques, the use of quantitative data analysis skills and computational tools, and showcasing the interdisciplinary nature of science. To ensure our cases capture the essence of HT discovery science, we crafted a set of learning objectives to ground our HT case study development (Supplementary Table S1). Our HT cases also often use publicly-available large, complex datasets to facilitate reproducibility studies (OSC, 2015) as well as authentic data mining (Hand, 2007). In addition to introducing students to databases/repositories and HT experimental design, a second focus of HT cases is to immerse students in the development of analytical skills (e.g., filter, analyze, and interpret data; synthesize data and draw appropriate inferences) with large, complex datasets. Williams et al. (2019) identified that faculty perceive barriers to integrating computational and bioinformatics competencies involving HT “big data” into curricula. HITS helps lower these barriers by offering validated case studies that can facilitate the execution of competency-based learning outcomes (e.g., analytical skills). HT cases also address the barriers of limited instructor training and lack of HT technology on many campuses. The use of publicly available datasets, instructor collaboration with experts, detailed implementation notes, and the modular and adaptable nature of HTS cases make them easy to adopt or alter to meet specific curricular learning goals. HT cases are also well suited for use in a variety of modalities including interactive face-to-face classrooms, collaborative distance learning, and the laboratory environment (Bixler et al., 2021). HT cases in the laboratory setting can also provide learning resources for HT computational biology and bioinformatics-centric experiments. Over recent decades, computational biology has shifted from being a set of tools used to support biological studies to its own discipline that often drives research programs, with physical experiments and field research playing an equal or supporting role (Yanai and Chmielnicki, 2017; Tapprich et al., 2021). This interdisciplinary (e.g., life science, computer science, mathematics, statistics) nature of HT cases promotes multidisciplinary knowledge within the classroom, providing students with practice synthesizing ideas in the context of the collaborative nature of science. Here we share several examples of successful implementation of HT cases in a broad range of institutions and courses (Table 1) as well as our model for HT case development.

The High-Throughput Discovery Science and Inquiry-Based Case Studies for Today’s Students Network Model for High-Throughput Case Study Development

The goals of the HITS network (Figure 1; go.ncsu.edu/hits) are to . . .

- Organize interdisciplinary annual workshops, create a virtual community, and publish educational resources to foster HT research and its integration into the classroom.
- Create novel working groups of researchers and educators to design, assess, and disseminate much needed quantitative biology case studies based on HT discovery research.
- Build a diverse consortium of institutions committed to implementing these quantitative educational tools in biology courses and curricula across the country and world.

HITS case Fellows: As seen in Figure 1 and Supplementary Figure S1, the HITS network provides networking, research, and training opportunities for a diverse group of undergraduates, graduate students, postdoctoral fellows, researchers, and educators. Participants from a myriad of institutions and backgrounds interact at meetings, bringing creative energy and varied expertise to make HT discovery science, bioinformatics tools, case study design, and large, complex datasets accessible. Key among our participants are the HITS case Fellows. Given the barriers to integrating HT data into curricula (e.g., time, bioinformatics training, case study familiarity), HITS provides structured time, accountability, training, professional development, and financial support to case fellows who commit to creating and implementing HT case studies. We support at least 10 new HITS case Fellows each year by providing their HT case study training (i.e., 2 years of stipends and the opportunity to participate in two annual HITS meetings free of cost). In turn HITS fellows collaborate in teams to build modular and adaptable HT case studies for a variety of classroom
| Case Title (and link), Authors, Case Description | Curricular and Student Impact |
|------------------------------------------------|-----------------------------|
| COVID-19: Where Did You Come From, Where Did You Go? Chen, S., Goller, C.C., Srougi, M.C. Focused on the evolution and spread of SARS-CoV-2 during the pandemic, students use freely available bioinformatics tools (NCBI, BLAST, NextStrain) to track changes in SARS-CoV-2 through its genetic code | N.C. State University (20–32 students) in either an introductory 100 level biotechnology course and a 400 level virus biotechnology course |
| Applying High-Throughput Analysis to Biofilms Homesley, Jr, M.L. This case uses a hypothetical scenario in which a dental practice is contaminated from an unknown bacterial source. Students determine the origin of the bacteria and learn about a high-throughput experiment for analyzing biofilms | This student-produced case serves as an example for other students to create and publish case studies that combine their research interests and high-throughput approaches. For example, this case inspired another student to create and publish a case study on their research |
| Does Organelle Shape Matter: Exploring Patterns in Cell Shape and Structure with High-throughput (HT) Imaging Goller, C.C., Casimo, K Using the Allen Cell Explorer, students study shape changes in the endoplasmic reticulum | N.C. State University (10–16 students) in upper-division genomics class every semester since Spring 2020 |
| Single Cell Insights into Cancer Transcriptomes: A Five-Part Single-Cell RNAseq Case Study Lesson SamSa, L., Eslinger, M., Kleinschmit, A., Sorelm, A., Goller, C Students experience how single cell RNA sequencing transcriptomics is used to discover novel ways that cells function in homeostasis and disease | N.C. State University (10–16 students in upper-division genomics class every semester since Spring 2020) University of Dubuque (24 students/semester- Spring 2020 and 2021) Hastings College (12 students) |
| Seq’ing the Cure: Standard Edition and Neuroscience Editions Miller, H.B., Robertson, S.D., Srougi, M.C. Students analyze RNA-seq data and identify differentially expressed genes in the context of a patient who presents at the ER with a neurological disorder | UNC Chapel Hill (>100 students across 3 semesters of a 400-level Neurotechnology course) High Point University (>10 students in Biochemistry II and 18 in Biochemistry of Gene Expression per semester) |
| New Tricks for Old Drugs: Using High-throughput Screening to Repurpose FDA-Approved Drugs to Combat Zika Virus Goller, C., Chen, S., Srougi, M Students explore a publication about Zika virus drug screen and use PubChem | N.C. State University (10–16 students in upper-level Genomics course every semester since Spring 2020) |
| Pesticides in My Smoothie Bowl? Yu, S., Weir, S Introduces basic concepts and processes of ecological and human health risk assessment using pesticides as an example and provides students an opportunity to analyze real-world pesticide monitoring data | Central Piedmont Community College (>30 students in Introductory Biology per semester) |
| What’s the Difference?: Differential Methylation Within Schizophrenia Simkin, A., Nedzialek, E., Eslinger, M Students examine the genetic methylation patterns of people with and without schizophrenia to identify potential candidate genes whose abnormal methylation may be associated with schizophrenia | West Point (>50 students over two semesters of 300-level Genetics) Elon University (>20 students in Genetics Lab) |
| Mapping Human Neuron Diversity in the Search for New Therapies Casimo, K. Robertson, S Students collect data from the Allen Cell Types Database, a resource by the Allen Institute for Brain Science, and evaluate the properties of neurons in the temporal lobe compared to other brain regions | UNC Chapel Hill (>200 students in 100 level introduction to neuroscience course and 400 level neurotech course) |
| Screening Nanobodies to Target Chen, S., Bieler, A Students learn techniques involved in directed evolution, particularly yeast surface display, in the context of research on SARS-CoV-2 | Clarke University (Introductory version tested with 18 intro students; an upper-level/ graduate version will also be available) |
| You Are What You Eat: Microbiome and Disease Carroll C., Dihle P., Salger S., Vega N., Gaudier-Diaz M., Kleinschmit A., Robertson Students explore high-throughput sequencing technologies used to study microbiota, factors to consider when designing microbiome studies, data processing and visualization of microbiome data, and societal considerations touching on ethical issues, which may lead to microbiome inequality | University of Dubuque (48 students in 300-level Microbiology class) UNC Chapel Hill (>100 students across 2 semesters of a 400-level Neurotechnology course) UNC Pembroke (18 students in a Physiology class) Emory University (15 students in an upper-level undergard/grad Microbiome Ecology class) West Point (>40 students in 3 sections of Genetics) |

(Continued on following page)
environments (Table 1). Our case Fellows also commit to validating the newly created HT cases through cycles of assessment and revision. Once validated, dissemination of the HT cases for broader use in the educational community is a key goal. To recruit HITS case Fellows, each year we advertise widely primarily through the QUBES platform (Donovan et al., 2015) and our collective listservs and professional networks. We leverage attendance and participation at various national meetings (e.g., NIBSE conference 2019; PANPBL 2019; NCCSTS 2018, BIOME 2018 and 2020). Now in our fourth year we’ve expanded to an international network that includes >80 members, and to date, we’ve supported >60 HITS participants from 34 institutions at our annual conference (Supplementary Figure S1).

HITS Annual Conference: The HITS conference occurs annually and has taken place both in person (2018 and 2019) and virtually due to the COVID-19 pandemic (2020 and 2021). The workshop’s three-day schedule has evolved over time but generally includes: 1) exposure to HT Discovery Science from research experts on day one, 2) interactive workshop sessions with case study experts and brainstorming of case ideas to facilitate team formation on day two, and 3) protected time for interdisciplinary teams to collaborate on cases on day three (Sample Schedule Supplementary Material 3). Key to the success of these workshop sessions is the active collaboration of HT researchers and case study development experts. HT scientists provide short talks and opportunities for case Fellows to learn about or work with large, complex HT datasets. To complement the HT training, pedagogical case study experts provide evidence-based best practices for case design and have participants work through exemplary case-based learning resources and tools.

Case Fellows participate in our HITS summer workshop twice, which allows them to first become familiar with HT research and case study development, and later gain confidence in their abilities to generate, implement, assess, and disseminate HT case studies. Given the conference format and their 2-year involvement, all fellows contribute to multiple cases. Indeed, interdisciplinary collaboration is key in the development of these HT case studies. Often, research experts familiar with the datasets or even responsible for generating them collaborate with classroom teachers to select and trim appropriate datasets as well as design case studies that can be implemented in a variety of courses. At the conference, case Fellows generate a list of HT topics which later narrows as teams are formed. Within each team tasks are distributed to lessen each instructor’s burden, ensuring the HT case is integrated into each classroom. Teams then have the opportunity to present at the conference and receive feedback from HT experts, other fellows, and case design experts. This piloting with both students and HITS participants alike enables rounds of revision to refine and validate the newly created HT case for assessment and broader dissemination, which includes student materials, detailed teaching notes, and in some cases cloud-based computing resources through QUBES.

The diverse perspectives among case Fellows ensures the development of cases that can be adapted to either introductory or advanced courses in a wide variety of topics (e.g., Neuroscience, Anatomy and Physiology, Genetics, Ecology, Biotechnology), broadening the impact of our network. During our conference there is also opportunity to discuss and address barriers to implementation (e.g., teaching load, class size, heterogeneity of student background and preparation). Modular design to enable adaptability for VERY different classrooms and virtual case Fellow support throughout the 2 years beyond the conference are key. This continued virtual collaboration to facilitate development, implementation, assessment, and dissemination is supported by QUBES (Donovan et al., 2015) and modeled by other successful
networks (Ryder et al., 2020). Our HITS website allows us to track case study team progress and to feature examples of newly created HT case studies. Access to collaborative teams and the virtual HT support network is essential to the success of each case Fellow and HITS participant. Indeed, the three-year evaluation of the program prepared by the NC State Office of Faculty Development found that 94% of prior year respondents published one or more cases since becoming a HITS case Fellow and 13% created ≥3.

HITS Steering Committee: HITS also relies on a senior leadership team composed of the PI, Co-PI and steering committee that analyzes report data to identify improvement ideas, suggests methods for network expansion, and promotes inclusivity. This team includes diverse faculty from all career levels and types of academic institutions (public and private, R1, primarily undergraduate, and minority serving institutions). The diversity of perspectives has enabled us to identify and adjust to major roadblocks in the development of the HTS network. Our steering committee has also shared their own HT research, led case study workshop sessions and interactive QUBES tutorials. Steering committee members work with individual teams of case fellows throughout each year to assist in continued virtual case study development, assessment and dissemination. The extensive networks of our steering committee team has also enabled us to coordinate with existing resources (ScienceCaseNet, QUBES, NIBLSE, BioQuest) to disseminate products and recruit interested faculty. The steering committee’s exemplary, strong, and diverse leadership is essential to meeting our call to integrate HT discovery science into life science education.

Discussion

Case studies based on authentic HT data present an untapped opportunity to engage students in the process of discovery while also teaching them fundamental quantitative reasoning skills. HITS has capitalized on the synergy between diverse HT researchers and educators to create such cases through interdisciplinary collaboration and professional development training opportunities at all levels. The accomplishments of HITS case Fellows are showcased in several publications as either open educational resources or as free resources with access to supplemental documents for a nominal fee depending on the outlet (Table 1). These cooperative teams leverage individual expertise to develop ambitious, often modular, cases for use across the nation. Our cases have immersed hundreds of students in cutting-edge HT-experimental approaches, which are transforming how biology research is conducted, all while ensuring students develop essential data literacy and quantitative skills. Such curricular reform establishes a shared community of ideas with themes that cross multi-disciplinary thresholds and incorporate our established shareholders.

Our network has developed a long-term sustainability plan to continue to generate high-impact, HT case studies. A growing awareness of HITS and our goals and sense of community are necessary to have a lasting impact (AAAS, 2011). In particular, this requires a clear identification of stakeholders, in our case, 1) HITS case Fellows (e.g., seasoned faculty, mid-career, new trainees) 2) researchers (e.g., science, technology, bioinformatics), 3) educators (undergraduate and graduate education) 4) curriculum specialists (educators, information technologists) and 5) partner organizations (e.g., HHMI, AAAS, SABER). Synergistic approaches with these stakeholders will widen the HITS aperture to support our organizational goals. Here are five key steps in our strategic plan to further integrate HT discovery science and bioinformatics skill development into life science curricula across the nation and internationally:

1. Recruit and develop enduring teams who commit to leveraging their interdisciplinary expertise in STEM-related fields and bioinformatics to integrate HT science into undergraduate and graduate curricula.
2. Identify and address barriers to implementing HT approaches in the classroom (e.g., faculty/student reluctance, technology, accessibility, language/terminology, perceptions).
3. Continue to create, validate, and share curriculum products that train other faculty and students in the acquisition, analysis, and discovery of the HT data sciences.
4. Encourage the diversity, equity, and inclusion of students and trainees in HT discovery science through the development of cutting-edge curricula that promote STEM retention and leadership of the next generation.
5. Expand the HITS network through broad dissemination of our goals and products as well as through strategic partnerships with key life science and bioinformatics educational communities.

Our network’s educational resources can be implemented in a variety of classrooms. Our HITS framework can also serve as a model for related fields with similar training bottlenecks to help create resources that address key gaps in current biology curricula. We also welcome collaboration to support other ongoing related initiatives (e.g., NIBSE, NEUBIAS, NUMB3RS COUNT!, EDDIE) and will continue to share products through publications, presentations, workshops, and open educational resources through QUBES. This will encourage adoption, adaptation, assessment, and creation of additional cases that use HT approaches and data to transform life science curricula and adequately equip our next generation of scientists with key quantitative and data science skills.

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DATA AVAILABILITY STATEMENT
Publicly available datasets were analyzed in this study. This data can be found here: go.ncsu.edu/hits.

AUTHOR CONTRIBUTIONS
All authors collaborated to create the manuscript. CG and SR lead the HITS network and led the development and publication of this manuscript. AB, ME, MG-D, AK, PM, KO’T, and US are all HITS participants, and all contributed significantly to the writing and development of the manuscript including figure and table creation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/feduc.2021.711512/full#supplementary-material

Supplementary Figure 1 | Distribution of HITS network across North America. The HITS network includes 77 participants from 35 institutions from 2018 to 2020. Each circle represents a unique academic, non-profit, or government institution. Size and color represent the number of participants from each institution. Represented institutions in alphabetical order: Adams State University, Alamanca Community College, Allen Institute for Science, Barton College, Campbell University, Carroll University, Central Piedmont Community College, Clarke University, Colorado State University, Davenport University, Elon University, Emory University, Fordham University, Hartford College, Hastings College, Heidelberg University, High Point University, Meredith College, Morehouse College, National Institute of Environmental Health Sciences (NIHES), New School, North Carolina Agricultural and Technical State University, North Carolina State University, Northwestern Connecticut Community College, Saint Augustine University, Salem College, Telus World of Science, Trinity Washington University, United States Military Academy West Point, University of Dubuque, University of New Haven, University of North Carolina at Chapel Hill, University of North Carolina at Pembroke, University of Pittsburgh, and University of Richmond.

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