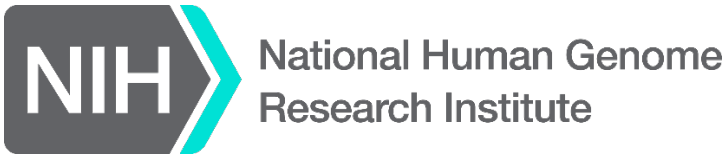

Report of the

2022 - 2023
Blue Ribbon Panel Review

of the

National Human Genome Research Institute
Intramural Research Program

May 2023

Background and Preamble:

The Intramural Research Program (IRP) of each NIH Institute/Center (IC) is required to undergo a review by a panel of outside experts ("Blue Ribbon Panel," or BRP) roughly every 10 years. These reviews aim to provide high-level feedback and general input about the current state and future opportunities of the various NIH IRPs, which complements the more detailed, investigator-by-investigator reviews that take place every four years by the institute/center's Board of Scientific Counselors.

The National Human Genome Research Institute (NHGRI) IRP was founded in 1993. It is currently associated with a total of 72 faculty (including Associate Investigators, Adjuncts, Senior Clinicians and Senior Scientists, as well as Investigators and Senior Investigators), a total staff of ~570, and an annual budget of $127M. The Program is now led by Dr. Charles Rotimi (Scientific Director); previous Scientific Directors were Dr. Jeffrey Trent (1993-2002), Dr. Eric Green (2002-2010), and Dr. Daniel Kastner (2010-2021). This is the third Blue Ribbon Panel review of the NHGRI IRP, the initial one being held in 2001 at a time when the program was still in a significant growth phase. It is notable that the current BRP review is being held at a distinctly different 'life phase' of the NHGRI IRP.

To review the NHGRI IRP, Dr. Eric Green (Director, NHGRI) convened a group of eight experts with a broad perspective on genetics and genomics and considerable knowledge about NHGRI (see attached roster of the BRP – **Appendix 1**). Drs. Gail Jarvik (University of Washington) and Lynn Jorde (University of Utah School of Medicine) co-chaired the BRP, which was convened from May 2022 to May 2023.

Specifically, NHGRI leadership requested that the Panel provide feedback and advice about the IRP, with a particular focus on the coming decade. The timing was ideal for this with the appointment of Dr. Charles Rotimi as the new NHGRI Scientific Director in 2021.

The review process consisted of the following elements:

- Five Virtual BRP meetings (May 31, 2022; September 6, 2022; February 17, 2023; April 11, 2023; April 20, 2023)
- Virtual meetings with various faculty members
- Five White Papers addressing 'big questions' developed by IRP Leadership and Faculty for Blue Ribbon Panel consideration
- A two-day in-person meeting on December 8-9, 2022 on NIH Campus in Bethesda, MD (see attached agenda – **Appendix 2**)

The BRP concluded that the above set of meetings and discussions provided the necessary information and other input for the overall assessment detailed below. Overall, the BRP has a highly favorable opinion of the NHGRI Intramural Research Program. IRP staff and faculty work well together, and NHGRI leadership is appreciated and well respected. The White Paper

process was extremely useful in summarizing proposed future directions for the IRP. As detailed in this document, the BRP generally supports the ideas proposed in the White Papers.

Assessment:

The science within the IRP is outstanding. The 72 IRP faculty members published 1,260 papers from 2018 to 2023 (see **Appendix 3**: Lin, Wang, and Koehly, Feb. 2023). Notably, 30% of these publications represented co-authorships with another NHGRI faculty member, reflecting a high degree of collaboration (see **Fig. 1**). Moreover, IRP faculty members co-published with faculty from an average of six other ICs, with an average of 18 collaborative publications per faculty member. NHGRI IRP faculty have co-published with investigators from 459 US institutions, representing all 50 states and Puerto Rico. They have co-authored publications with investigators from 102 countries across the world.

In the BRP's view, the IRP faculty are generally happy with the resources and trajectories of their research groups. Across the NIH, the IRP is viewed as innovative, forward-looking, and collaborative. Despite a modest budget relative to most other ICs, IRP scientists are accomplishing a great deal of high-quality research. A number of issues and challenges that face the IRP in coming years are discussed in detail in the following sections.

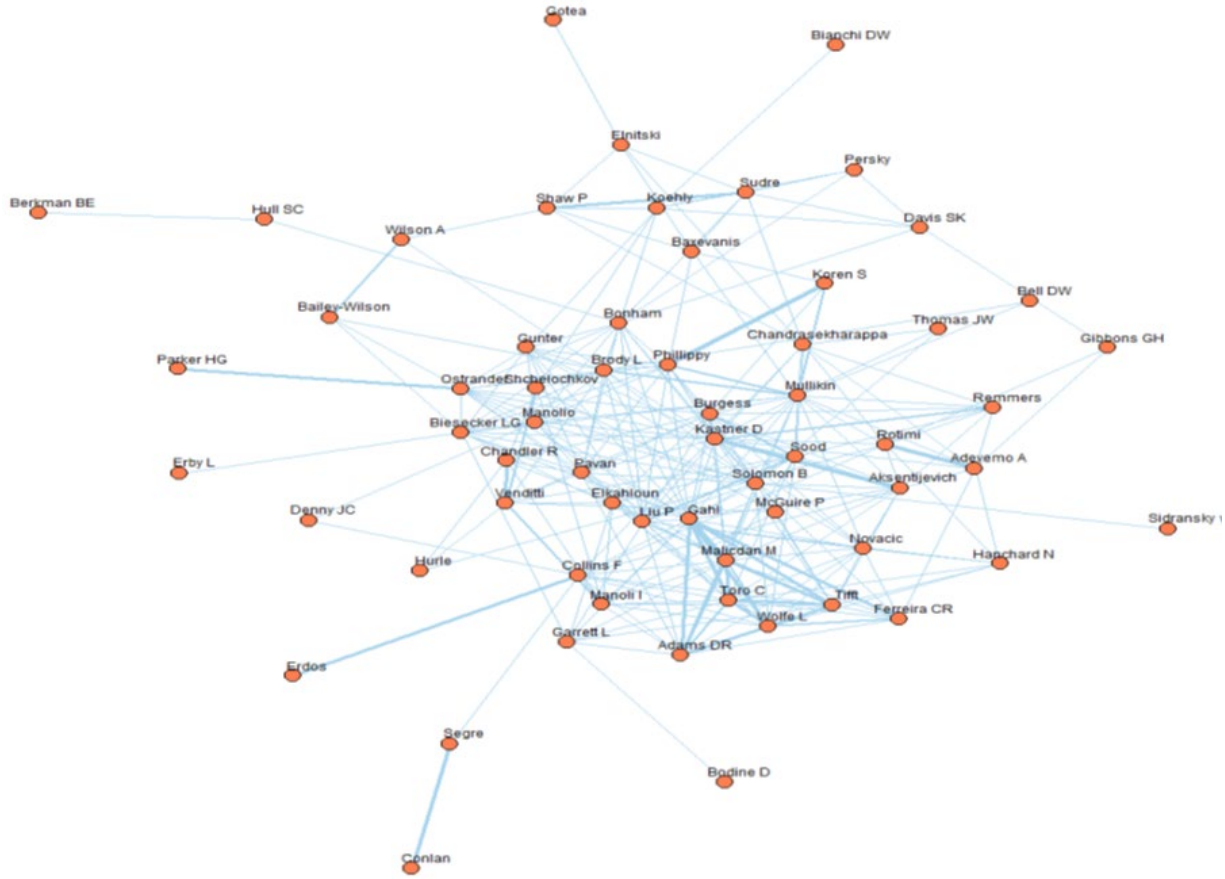

Figure 1: Interactome showing co-authorships among IRP faculty

Recommendations:

Direction:

The NHGRI IRP has a long history of groundbreaking – even paradigm-shifting – genomic research. It should strive to continue this trajectory in developing and applying genomic approaches for the prediction, diagnosis, prevention, and treatment of disease. The IRP is a world leader in the study and treatment of rare diseases (exemplified by the highly successful Undiagnosed Disease Program and gene therapy efforts), and this should be maintained. At the same time, increasing attention is being paid to the genetics of more common conditions, such as heart disease, common cancers, and diabetes. There is a growing appreciation of the potential for rare disease studies to inform our understanding of common diseases. Based on its track record, faculty, and leadership, the IRP is well-positioned to expand the way in which genomic investigation of rare and common diseases inform one another.

Some examples of areas in which the IRP can be leaders include:

- As exome and whole-genome sequencing become commonplace, a "genotype first" approach can be adopted to analyze and classify diseases.
- Polygenic risk scores have been developed for nearly all common diseases, but further analysis and validation is needed before they can be usefully applied in clinical settings. The IRP can play a major role in developing and applying risk scores (using both genetic and nongenetic data) in diverse human populations.
- Multi-omic analysis is proving to add considerable interpretive power to genomic data and should be further developed.
- All advances in genetics and genomics involve generation of huge amounts of data. The planned Center for Genome Data Science can enable NHGRI to be a leader in advanced data analysis.

These goals can be accomplished while avoiding duplication of efforts at programmatic ICs (e.g., NHLBI, NCI, NIAID, NIDDK) and by coordinating with efforts at other ICs. By spearheading "omics" approaches to understanding both rare and common diseases, the IRP can promote collaboration across NIH and with institutions across the country.

A common issue in biomedical science is the appropriate balance between basic and translational research. The IRP has strength in both these areas; maintaining a proper balance will be an important consideration as some senior faculty enter the autumns of their careers. This will be a complex and challenging decision-making process, and all faculty should have opportunities to participate in it. Also, it should be recognized and appreciated that "basic" and "translational" science are by no means discrete categories – many or most scientists are involved in both areas.

The NIH Clinical Center (CC) was the subject of much conversation. It is recognized as a truly unique resource with opportunities for deep phenotyping, genome sequencing, and longitudinal follow-up. Yet its potential does not seem to be fully realized. The IRP should consider novel ways in which to take full advantage of the CC's resources, samples, and data.

Recruitment:

As the IRP continues to evolve, recruitment of top-notch faculty and staff is a key priority. The IRP should continue to focus on recruitment of outstanding, team players who can leverage NHGRI's many strengths in all areas of genomics. Several translational/clinical faculty are likely near retirement, and they have built considerable resources during their careers (data, samples, etc.). Notably, 90% of patients seen in the NHGRI Clinical Program were supervised by PIs who are eligible for retirement. New faculty recruits in this area should carry on the outstanding traditions of collaborative translational and clinical research while taking full advantage of the resources that have been built. Recruitment of both basic and translational scientists should emphasize faculty who can easily and willingly bridge the two areas and whose research goals are aligned with NIH's mission.

An unavoidable challenge in attracting top faculty recruits is the federal pay scale. However, potential recruits should be reminded of the many advantages unique to the NHGRI IRP. These include ready access to the CC, the freedom to explore research areas that might be considered too adventurous or long-term by NIH's extramural program, a relatively high level of job security, and – most important of all – employment in the NIH itself, the world's foremost biomedical research organization.

Collaboration:

While the IRP should be justifiably proud of its record of collaboration, the BRP identified areas in which even more interactions can be pursued:

- Despite much commonality between NHGRI and the All of Us Research Program, the two seem somewhat disconnected from one another. The BRP recommends increasing the frequency and intensity of this potentially fruitful collaboration.
- The IRP should be a leader in promoting open, transparent sharing of data (including All of Us) across the NIH.
- The IRP, especially with the new Center for Genomic Data Science, should take a leading role in integrating data science efforts (especially those involving genomics) across all NIH ICs.
- Strengthen the relationship between the IRP and NHGRI's education efforts. Biomedical science is in dire need of more well-trained genome scientists, and the IRP could aid in helping to meet this need.

- Improve local community engagement. There are substantial opportunities for local engagement in Washington, D.C., (e.g., community hospitals and healthcare systems).

Diversity:

The committee was impressed by the diversity efforts demonstrated or planned by the NHGRI IRP. We urge the IRP to continue to strive to improve and increase diversity in all its efforts, including workforce recruitment, training, and research participants. Community engagement, including your local community, should be further explored.

Policies/Procedures:

The BRP was unanimous in its strong commitment to data sharing. We applaud the NHGRI for their leadership in extramural data sharing. We strongly support the sharing of IRP data. IRP investigators should be subject to the same data sharing rules as extramural investigators. Another opportunity for shared data and resources would be a bio repository for the IRP. A bio repository with demonstrated sample quality could benefit many investigators. Additionally, inclusion in a bio repository of samples from retiring investigators would assure that these valuable samples are available for future research efforts.

New initiatives/leadership:

In response to presentations made to us by NHGRI IRP faculty and our subsequent discussions, the BRP wishes to express particular enthusiasm for the following proposals or suggestions.

- Launch a Center for Genomic Data Science to grow and maintain the IRP's leadership in genomic data science. NHGRI IRP is well positioned for leadership in this area and can take advantage of current strengths and new recruitment to further build this program. Such a Center would also be a perfect opportunity for interactions with other NIH ICs and collaborators outside of NIH.
- Expanding computational scientist development by developing a formal Computational Scientist Development Program (CSDP). Commitment to the training and support for computational biology, data sciences, bioinformatics, statistics, and genomics at all levels would complement the Genomic Data Science Center and be in important contribution to the field.
- Sequencing of NIH CC patient participants. One of the possible initiatives that IRP faculty brought to the BRP is the sequencing of some or all NIH CC patients. The BRP suggests exploring a partnership with the All of Us Research Program to sequence all those NIH CC patients whose data can be shared. As noted previously, we believe that data sharing should be an important value of the IRP. We assume that partnering with All of Us would require data sharing. If budget constraints limit the opportunity to sequence NIH CC patient participants, we suggest that priorities be set based on patient phenotypes and likelihood that genomic data will be useful.

- Integration of genomic data in the EHR. The BRP considers the poor integration of genomic data into electronic health records (EHRs) to be an obstacle to implementation of genomic medicine. Can the IRP take a leadership role in integrating genomic data in commercial EHRs? We recognize that the use of a noncommercial EHR at the NIH CC may be a limitation; however, this type of activity would fit with the IRP's leadership in data science.
- Training. The IRP has an outstanding environment for trainees and a laudable commitment to diversity and inclusion. Making diverse and inclusive professional development an integral part of training and implementing mentorship training for faculty and senior staff should be a continued priority. This should include building evaluation capability to measure the effects of training program changes and enable evidence-based decision-making by institute leaders.

In conclusion, the NHGRI IRP is an impressive success. The faculty and trainees are highly productive. The level of science is outstanding. Productivity is remarkable, especially given the budget. There is a growing and sincere dedication to diversity and inclusion. All of this speaks to excellence in leadership. We have outlined opportunities for the IRP; we acknowledge that there are fiscal challenges beyond the control of NHGRI that require prioritization of new initiatives. We look forward to the next 10 years of your shared success.

Appendix 1

2022-2023 Blue Ribbon Panel Review
NHGRI Intramural Research Program
Panel Roster

Gail Jarvik, M.D., Ph.D. (Co-Chair)
The Arno G. Motulsky Endowed Chair in Medicine
Professor and Head, Division of Medical Genetics
University of Washington

Lynn Jorde, Ph.D. (Co-Chair)
Mark and Kathie Miller Presidential Professor and Chair
Department of Human Genetics
University of Utah School of Medicine

Greg Barsh, M.D., Ph.D.
Faculty investigator and Faculty Chair
Smith Family Chair in Genomics
HudsonAlpha Institute for Biotechnology

Lon Cardon, Ph.D.
President and CEO
The Jackson Laboratory

Chanita Hughes-Halbert, Ph.D.
Associate Director, Cancer Equity
Norris Comprehensive Cancer Center
Keck School of Medicine
University of Southern California

Guillermina (Gigi) Lozano, Ph.D.
Hubert L. Olive Stringer Distinguished Chair in Oncology in Honor of Sue Gribble Stringer
Department of Genetics, Division of Basic Science Research
University of Texas MD Anderson Cancer Center

Carole Ober, Ph.D.
Chair of Human Genetics
Blum-Riese Distinguished Service Professor of Human Genetics
The University of Chicago

Neil Risch, Ph.D. (Liaison to the Advisory Committee to the NIH Director)
Lamond Family Foundation Distinguished Professor in Human Genetics
University of California, San Francisco

Appendix 2

NHGRI Blue Ribbon Panel In-Person Meeting
December 8-9, 2022
AGENDA

December 8, 2022

9:00 am	Transportation from Hyatt Regency Bethesda to NIH Campus Meeting location: NHGRI Conference Room, Building 31, Room 4B31
9:30 am	Executive Session • Discuss plans for the next two days • Discuss Zoom meetings with individual investigators • Formulate major issues to discuss • Other topics to discuss?
11:00 am	Discussion of White Paper #1: Leslie Biesecker, M.D., Elaine Ostrander, Ph.D.
11:45 am	Break
12:00 pm	Discussion of White Paper #3: Teri Manolio, M.D., Ph.D., Benjamin Solomon, M.D.
12:45 pm	Working Lunch and Executive Session
1:30 pm	Training, Diversity and Health Equity Office (TiDHE) and the NHGRI Intramural Research Program: Vence Bonham, J.D.
2:00 pm	Discussion of White Paper #5: Vence Bonham, J.D., Laura Koehly, Ph.D.
2:45 pm	Break
3:00 pm	Check in and Open Discussion: Eric Green, M.D., Ph.D. and Ellen Rolfes, M.A.
3:30 pm	Break
3:45 pm	Discussion with NIH Scientific Directors & Clinical Directors (Virtual) ▪ Stephen Chanock, M.D., Scientific Director, Division of Cancer Epidemiology & Genetics, NCI ▪ John Gallin, M.D., Chief Scientific Officer and Scientific Director of the NIH Clinical Center ▪ Steven Holland, M.D., Director, Division of Intramural Research, NIAID ▪ Janice Lee, D.D.S., M.D., M.S., Clinical Director, NIDCR ▪ John O'Shea, M.D., Scientific Director, NIAMS ▪ Sharon Savage, M.D., Clinical Director, Division of Cancer Epidemiology & Genetics, NCI
4:30 pm	Nina Schor, M.D., Ph.D., NIH Deputy Director for Intramural Research

5:00 pm Executive Session

6:00 pm Return to Hotel

7:00 pm Group Dinner at Bacchus, 7945 Norfolk Ave, Bethesda, MD

December 9, 2022

8:30 am Transportation from Hyatt Regency Bethesda to NIH Campus
Meeting location: NHGRI Conference Room, Building 31, Room 4B31

9:00 am Why don't all patients at the NIH Clinical Center get their genomes sequenced?
Leslie Biesecker, M.D., Benjamin Solomon, M.D.

10:00 am Discussion of White Paper #2: William Gahl, M.D., Ph.D., Ellen Sidransky, M.D., Daniel Kastner, M.D., Ph.D.

10:45 am Break

11:00 am Discussion of White Paper #4: William Pavan, Ph.D., Julie Segre, Ph.D., Faith Harrow Plante, Ph.D.

12:00 pm Working Lunch and Executive Session

1:00 pm Exit Interview with NHGRI Leadership
- Vence Bonham, J.D.
- Eric Green, M.D., Ph.D.
- Paul Liu, M.D., Ph.D.
- Ellen Rolfes, M.A.
- Charles Rotimi, Ph.D.

2:00 pm Adjourn and Departures

Appendix 3

Collaboration Networks of NHGRI IRP

Jielu Lin, Helen Wang, & Laura Koehly

Feb 10, 2023

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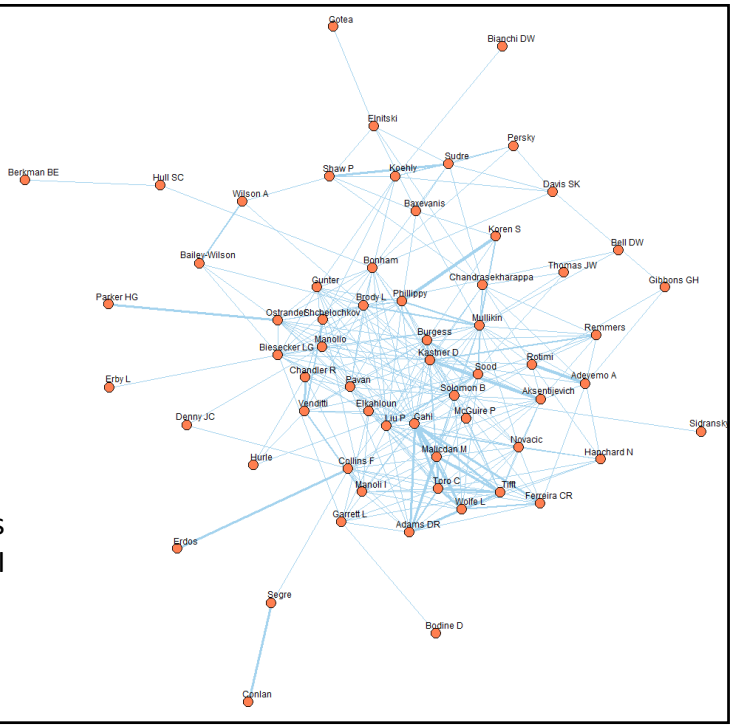
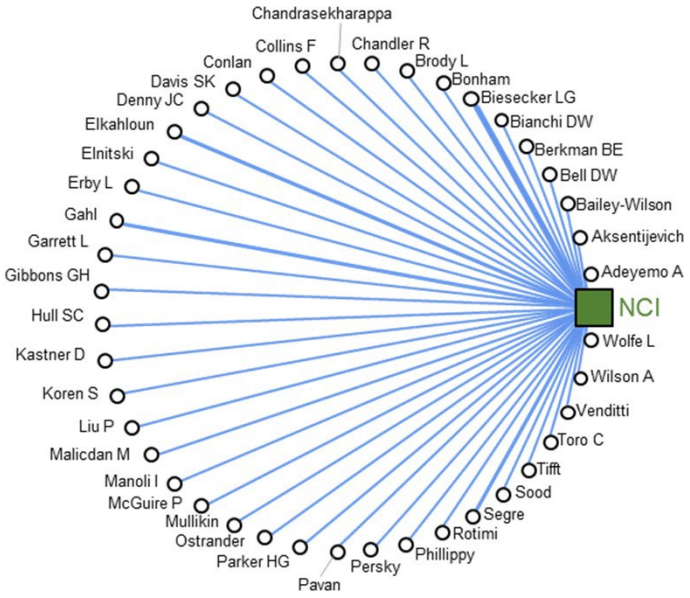
Within NHGRI IRP

- In 2018-2023, 62 (out of 65) faculty members authored 1,260 publications.
- 374 publications, or 30%, involves collaboration with another NHGRI IRP faculty member



Within NIH

- NHGRI IRP faculty have co-published with **ALL NIH ICs** (expect for Fogarty) and OD
- For example, 43 NHGRI IRP faculty members have co-published with researchers from NCI
- Thicker lines indicate more publications
- Average # of collaborating ICs per faculty member: **6**
- Average # of collaborative publications per faculty member: **18**



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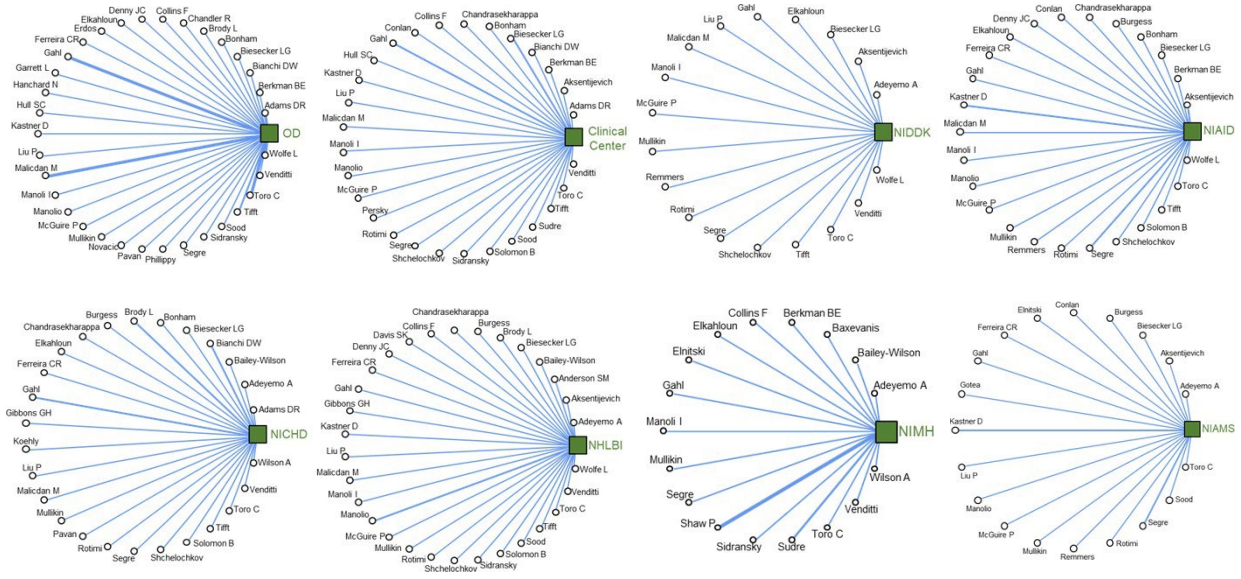
Within NIH Collaborations (cont.)



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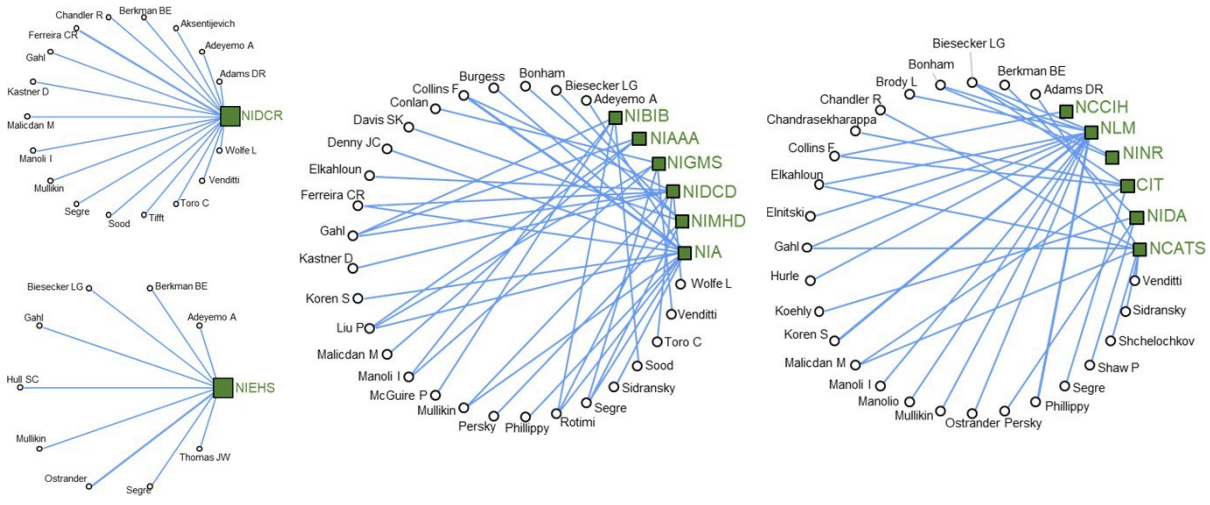
Within NIH Collaborations (cont.)



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Number of NHGRI Faculty Collaborating with Another IC, 2018-2023, by IC

IC	No. NHGRI Faculty	IC	No. NHGRI Faculty
NCI	42	NIA	12
OD	33	NIDCD	9
NHLBI	30	NIEHS	9
CC	28	NCATS	8
NICHD	26	CIT	5
NIAID	25	NIBIB	5
NEI	22	NIGMS	5
NIAMS	19	NIMHD	5
NIDDK	18	NIDA	4
NIDCR	17	NIAAA	3
NIMH	17	NINR	2
NINDS	17	CSR	1
NLM	13	NCCIH	1

Number of ICs Collaborated With, 2018-2023, by NHGRI IRP Faculty

Name	No. Colab. IC	No. Colab. Pub	Name	No. Colab. IC	No. Colab. Pub	Name	No. Colab. IC	No. Colab. Pub
Adams DR	7	28	Erby L	1	4	Parker HG	1	1
Adeyemo A	9	22	Erdos	1	2	Pavan	4	11
Aksentijevich	7	32	Ferreira CR	10	30	Persky	4	9
Anderson SM	2	2	Gahl	18	123	Phillippy	4	22
Bailey-Wilson	6	14	Garrett L	2	5	Remmers	3	8
Baxevanis	1	1	Gibbons GH	3	4	Rotimi	10	16
Bell DW	1	1	Gotea	1	1	Segre	15	49
Berkman BE	8	20	Hanchard N	1	1	Shaw P	2	24
Bianchi DW	4	14	Hull SC	4	7	Shchelochkov	6	7
Biesecker LG	14	63	Hurle	1	2	Sidransky	8	18
Bonham	8	13	Kastner D	9	46	Solomon B	5	9
Brody L	5	14	Koehly	2	3	Sood	8	15
Burgess	5	8	Koren S	3	17	Sudre	2	14
Chandler R	4	7	Liu P	10	20	Thomas JW	2	2
Chandra-sekharappa	6	8	Malicdan M	13	59	Tifft	11	42
Collins F	10	31	Manoli I	13	23	Toro C	13	61
Conlan	5	11	Manolio	6	17	Venditti	12	21
Davis SK	3	4	McGuire P	10	20	Wilson A	4	5
Denny JC	6	13	Mullikin	15	36	Wolfe L	9	31
Elkahloun	10	35	Novacic	2	5			
Elnitski	4	4	Ostrander	3	14			

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Outside NIH, in US

- NHGRI IRP faculty have co-published with 459 US institutions and organizations outside of NIH
- Collaborations in all 50 states and Puerto Rico
- Most are research universities and hospitals

Top 20 US Collaborators

Institution	No. NHGRI IRP Faculty	No. Colab. Pub.
Johns Hopkins University	38	173
Stanford University	37	110
Harvard University	36	210
Baylor College of Medicine	34	179
Duke University	33	46
University of Pennsylvania	32	108
Columbia University	31	75
UCSF	30	96
UCLA	29	99
University of Washington	28	229
University of Pittsburgh	27	59
Vanderbilt University	27	121
University of Texas	25	83
Mayo Clinic	24	89
Washington University in St. Louis	24	95
Boston Children's Hospital	23	88
New York University	23	55
University of Alabama at Birmingham	23	39
University of Maryland	23	77
Children's Hospital of Philadelphia	22	79

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Diversity in Extramural Collaborations Within US

- Federal agencies:
  - FDA, USDA, Walter Reed, VA
  - Smithsonian, Yellowstone, NOAA National labs
- State Health Departments
- Non-profit research:
  - RTI, Fred Hutchinson
  - Chan Zuckerburg Biohub
  - San Diego Zoo
- HBCUs: Howard, Florida A&M
- Patient advocacy groups
- Healthcare Providers
  - Kaiser, Geisinger
- Private Sector:
  - Merck, GSK, Pfizer, Eli Lilly
  - Illumina
  - Google, Microsoft
  - Biotech startups

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Outside US

- NHGRI IRP as a whole have co-published with researchers from 102 countries
- Number of co-publications is largely a function of number of research institutions in each country
- Consortium papers have many international collaborators

Country	No. Pub.	Country	No. Pub.	Country	No. Pub.	Country	No. Pub.
UK	213	Nigeria	23	Kenya	6	Belarus	1
Canada	135	Russia	23	Philippines	6	Benin	1
Germany	135	Estonia	21	Barbados	5	Costa Rica	1
Australia	107	Poland	20	Cyprus	4	Cuba	1
Netherland	105	Korea	19	Ethiopia	4	Faroe	1
France	88	Croatia	18	Gambia	4	Georgia	1
Italy	85	Hongkong	18	Armenia	3	Grenada	1
China	76	Iceland	17	Bangladesh	3	Ivory Coast	1
Switzerland	63	Pakistan	17	Burkina	3	Kazakhstan	1
Sweden	55	Ghana	16	Colombia	3	Luxembourg	1
Denmark	51	Uganda	14	Hungary	3	Mali	1
Japan	50	Taiwan	14	Indonesia	3	Moscow	1
Spain	50	Mexico	13	Lithuania	3	Nepal	1
Finland	49	New Zealand	13	Mauritius	3	Palestine	1
Israel	44	Kuwait	12	Morocco	3	Panama	1
India	37	Egypt	10	Romania	3	Paraguay	1
South Africa	37	Iran	10	Salvador	3	Peru	1
Brazil	35	Portugal	10	Serbia	3	Senegal	1
Ireland	35	Qatar	10	UAE	3	Slovenia	1
Belgium	34	Argentina	9	Malawi	2	Tanzania	1
Singapore	34	Sri Lanka	9	Botswana	2	Ukraine	1
Norway	32	Chile	8	Guinea	2	Venezuela	1
Saudi Arabia	32	Malaysia	8	Jamaica	2	Vietnam	1
Austria	31	Czech	7	Liechtenstein	2	Zambia	1
Turkey	24	Thailand	7	Rwanda	2		
Greece	23	Bulgaria	6	Tunisia	2		

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