

# International Network of Twin Registries (INTR): Building a Platform for International Collaboration

Dedra Buchwald,<sup>1</sup> Jaakko Kaprio,<sup>2,3,4</sup> John L. Hopper,<sup>5</sup> Joonhng Sung,<sup>6</sup> Jack Goldberg,<sup>7,8</sup>  
Isabel Fortier,<sup>9</sup> Andreas Busjhan,<sup>10</sup> Athula Sumathipala,<sup>11,12,13</sup> Wendy Cozen,<sup>14</sup> Thomas Mack,<sup>14</sup>  
Jeffrey M. Craig,<sup>15,16</sup> and Jennifer R. Harris<sup>17</sup>

<sup>1</sup>University of Washington Twin Registry, Departments of Epidemiology and Medicine, University of Washington, Seattle, WA, USA

<sup>2</sup>Finnish Twin Cohort Study, Department of Public Health, University of Helsinki, Hjelt Institute, Helsinki, Finland

<sup>3</sup>National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Helsinki, Finland

<sup>4</sup>Institute for Molecular Medicine (FIMM), University of Helsinki, Helsinki, Finland

<sup>5</sup>Australian Twin Registry, School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia

<sup>6</sup>Korean National Twin Registry and the Healthy Twin Study, Department of Epidemiology, Seoul National University School of Public Health, Seoul, Korea

<sup>7</sup>Vietnam Era Twin Registry, Seattle VA Epidemiologic Research and Information Center, Seattle, WA, USA

<sup>8</sup>Department of Epidemiology, University of Washington, Seattle, WA, USA

<sup>9</sup>Maelstrom Research, Research Institute of the McGill University Health Center, Montreal, Canada

<sup>10</sup>Humboldt University, Berlin, Germany

<sup>11</sup>Sri Lankan Twin Registry, Institute for Research and Development, Colombo, Sri Lanka

<sup>12</sup>Research Institute for Primary Care and Health Sciences, Faculty of Health, Keele University Staffordshire, UK

<sup>13</sup>Institute of Psychiatry, Kings College, London, UK

<sup>14</sup>Departments of Preventive Medicine and Pathology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

<sup>15</sup>Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Victoria, Australia

<sup>16</sup>Department of Paediatrics, The University of Melbourne, Melbourne, Victoria, Australia

<sup>17</sup>Norwegian Twin Registry, Division of Epidemiology, The Norwegian Institute of Public Health, Oslo, Norway

The International Network of Twin Registries (INTR) aims to foster scientific collaboration and promote twin research on a global scale by working to expand the resources of twin registries around the world and make them available to researchers who adhere to established guidelines for international collaboration. Our vision is to create an unprecedented scientific network of twin registries that will advance knowledge in ways that are impossible for individual registries, and includes the harmonization of data. INTR will also promote a broad range of activities, including the development of a website, formulation of data harmonization protocols, creation of a library of software tools for twin studies, design of a search engine to identify research partners, establishment of searchable inventories of data and biospecimens, development of templates for informed consent and data sharing, organization of symposia at International Society of Twin Studies conferences, support for scholar exchanges, and writing grant proposals.

■ **Keywords:** twin registries, twin research, international network, worldwide twins, collaborations, global studies

## Aims and Rationale

The International Network of Twin Registries (INTR) aims to foster scientific collaboration and promote twin research on a global scale. To this end, the INTR is working to expand the resources of twin registries around the world and make them available to researchers who adhere to established guidelines for international collaboration. As members of a working group of the International Society of Twin Studies (ISTS), our vision is to create an unprecedented scientific network of twin registries that will advance knowledge

of complex phenotypes. This network is intended to catalyze genomic and post-genomic research in ways that are impossible for individual registries, given the numbers of twin pairs needed for discovery and replication of findings.

RECEIVED 5 September 2014; ACCEPTED 10 September 2014.

ADDRESS FOR CORRESPONDENCE: Dedra Buchwald, MD, Departments of Epidemiology and Medicine, University of Washington Twin Registry, Seattle, WA, USA. E-mail: [dedra@u.washington.edu](mailto:dedra@u.washington.edu)

Further, the establishment of the INTR might well attract scientists who have not previously used twin designs but whose research would benefit from utilizing their unique potential.

Progress toward understanding the genetic and environmental underpinnings of health and disease can be accelerated by international, multi-registry collaborative research. Our vision for the INTR builds upon the fundamental principles underlying the harmonization of large-scale biobanks (Harris et al., 2012) and consortium studies (Boffetta et al., 2007). It requires openness, sharing, and synergy. This effort will accelerate the ability of the twin research community to conduct meta-analyses; it will provide a common platform from which twin pairs discordant for specific outcomes or exposures can be identified, and foster the secure exchange and analysis of individual-level data to conduct more complex investigations such as studies of the relationship between disease, environment, lifestyle and genes.

The INTR will also promote a broad range of activities, including the development of a website, formulation of data harmonization protocols, creation of a library of software tools for twin studies, design of a search engine to identify research partners, establishment of searchable inventories of data and biospecimens, development of templates for informed consent and data sharing, organization of symposia at ISTS conferences, support for scholar exchanges, and writing grant proposals for twin research.

Since the inception of the INTR, we have been mindful of the ethical issues presented by large-scale international research. We also recognize that many international partners operate in resource-poor settings that pose challenges above and beyond those encountered in well-funded environments. The INTR encourages the twin community to draw on the principles and tools developed by international data sharing initiatives (Knoppers et al., 2011; Knoppers et al., 2013; Knoppers et al., 2014) to address these issues.

## Website

Among the first priorities of the INTR was to establish a website ([www.worldwidetwins.net](http://www.worldwidetwins.net)) to facilitate communication and collaboration between registries and researchers within and outside the twin research community. The site includes a communication portal that facilitates discussions between researchers and registries that could generate new research, a blog about INTR activities, and links to useful tools and other resources. The website's functionality will be enhanced over time to meet the needs of our collaborators. Using information from the special issue of *Twin Research and Human Genetics* in February 2013, we systematically identified and contacted all known twin registries and invited them to nominate a contact person for listing on the website and a lead person for the site-enabled communications. One of our current projects is to review the type,

size, and processing of biospecimens collected by the registries we identified in this way. Results will be posted on the site.

## A Brief History of the INTR

After the ISTS meeting in Seoul in 2010, investigators from several twin registries established an ISTS working group to promote an international network of registries. Its first meeting was in March 2011 at the University of Melbourne in Australia. In December 2011, members of the working group developed a funding proposal in response to a solicitation by the U.S. National Institutes of Health for applications for the Director's Transformative Research Award. Twin registries worldwide were invited to participate in the proposal, entitled 'An International Network of Twin Registries for Epidemiological Studies', abbreviated as INTREPID (D. Buchwald, Principal Investigator). The application was submitted in January 2012. Although it was not funded, this effort generated enormous enthusiasm among twin registries to support and participate in such a network. Twenty-six registries representing 570,732 twin pairs in Asia, Europe, Australia, and North America endorsed INTREPID's dual goals of scientific collaboration and data harmonization.

In 2012, the Korean and Finnish twin registries were independently awarded research grants that included support for the INTR to host a two-day meeting at Seoul National University in Korea in May 2013. Attendees included 50 participants representing 25 twin registries in 20 countries (see [www.worldwidetwins.net](http://www.worldwidetwins.net)). The INTR working group also organized a symposium at the 43rd Annual Meeting of the Behavioral Genetics Association in Marseille, France, in June 2013. There we summarized the outcomes of the Seoul meeting in May and provided a forum for twin researchers to discuss their approaches to harmonizing data across multiple registries.

Our working group also holds regular conference calls, supported by the Korean grant, and our membership keeps growing. As our operations to date have been financed solely by awards to individual investigators, one of our principal goals is to secure the long-term funding needed to build and sustain a productive international network.

## Participating in INTR Initiatives

The INTR is open to all twin registries, and we especially encourage newly established registries to participate. Registries are asked to specify a contact person. The administrative structure of the INTR is simple, but it will likely evolve in response to funding mechanisms. Each registry will maintain control and responsibility for its own data and will make independent decisions regarding participation in each INTR initiative that arises. In addition, individual researchers can use and contribute to the resources accessible through the INTR, including the website. Although ISTS

membership is not required for collaboration, we encourage all researchers who use these resources to join ISTS.

## Summary

The INTR is a scientific network of twin registries that will greatly advance understanding of the role of genetics and environment in human health and illness. This is a propitious time to establish such a network, because innovations in genetics and genomics have made twin studies more valuable than ever (Boomsma et al., 2002; van Dongen et al., 2012). The INTR will enhance research on similarities and differences within and between twin pairs, especially research using the discordant monozygotic design. A very large sample of twins from around the world — one that is diverse not only in geography but also in culture, ethnicity, and genetic background — will help answer scientific questions that could not otherwise be broached. The richer and larger sets of twin data that could be available to collaborations, and the increased potential to recruit twins to new studies will enable the twin research community to capitalize on the latest omic technologies. We anticipate that their explorations will include studies of genetic, environmental and epigenetic determinants of disease risk. Given the availability of INTR data and resources, such studies will benefit from samples large enough to ensure robust conclusions. With adequate support, then, the INTR could have a major positive impact on public health, while building on the best traditions of team science.

The INTR recognizes that large-scale initiatives across diverse populations pose ethical challenges. As the INTR researchers develop collaborations, their practice must be guided by fair and transparent principles. An example is the framework for multinational research proposed by Emanuel et al. (2000). Building on this work, we offer the following criteria for INTR efforts: clear social and scientific value, rigorous scientific validity, favorable risk/benefit ratio, independent review, fair selection of research participants, informed consent and respect for all participants, and truly equal partnerships among researchers, policymakers, and communities (Emanuel et al., 2004).

The INTR intends to be flexible in responding to the interests of the broader scientific community. It will enable collaboration by researchers from varied backgrounds, regardless of their experience in twin studies. This approach will nurture truly translational science that integrates biochemical, genetic, clinical, behavioral, epidemiological, and twin research methodologies. It will also assist in recruiting and training the next generation of twin researchers, while disseminating a new understanding of twin studies among scientists across a range of disciplines.

Fostering international cross-cultural collaborations and open sharing of knowledge and experience is a key challenge for scientific discovery in the 21st century. An equally

formidable challenge is to sustain such collaborations over the long term. The INTR represents our best effort to meet both of these challenges. However, this network can fulfill its promise only if it can convince major funding agencies of the value of durable research infrastructures that span borders and continents.

The INTR invites the global research community to tackle the critical issue of sustainability. One approach would be to coordinate grant applications so that they allot a portion of their funding to support INTR services and thus help to build and sustain network activities. This approach would enable the INTR not only to thrive, but to continually optimize its utility to the scientific community.

For the near term, the INTR will keep pursuing funding opportunities to support its activities, including further development of the website to link network participants to each other and to the larger scientific community. In the longer term, it will build the website into a forum to link researchers with the participating twins who so generously donate their time and information, and in some instances bodily samples, to research.

## Acknowledgments

This work was supported by the National Research Foundation of Korea (grant #2011-220-E00006) and the Academy of Finland (grants #265240 and 263278). We thank Raymond Harris, PhD, for assistance in drafting the manuscript.

## References

- Boffetta, P., Armstrong, B., Linet, M., Kasten, C., Cozen, W., & Hartge, P. (2007). Consortia in cancer epidemiology: Lessons learned from InterLymph. *Cancer Epidemiology, Biomarkers and Prevention*, 16, 197–199.
- Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Review Genetics*, 3, 872–882.
- Emanuel, E. J., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *Journal of the American Medical Association*, 283, 2701–2711.
- Emanuel, E. J., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*, 189, 930–937.
- Harris, J. R., Burton, P., Knoppers, B. M., Lindpaintner, K., Bledsoe, M., Brookes, A. J., . . . Zatloukal, K. (2012). Toward a roadmap in global biobanking for health. *European Journal of Human Genetics*, 20, 1105–1111.
- Knoppers, B., Chisholm, R., Kaye, J., Cox, D., Thorogood, A., Burton, R., . . . Stolk, R. (2013). A P3G generic access agreement for population genomic studies. *Nature Biotechnology*, 31, 384–385.

- Knoppers, B. M., Harris, J. R., Budin-Ljosne, I., & Dove, E. S. (2014). A human rights approach to an international code of conduct for genomic and clinical data sharing. *Human Genetics, 133*, 895–903.
- Knoppers, B., Harris, J., Tasse, A., Budin-Ljosne, I., Kaye, J., Deschenes, M., . . . Zawati, M. N. (2011). Towards a data sharing code of conduct for international genomic research. *Genome Medicine, 3*, 46.
- van Dongen, J., Slagboom, P. E., Harmen, , Draisma, H. M. H., Martin, N. G., & Boomsma, D. I. (2012). The continuing value of twin studies in the omics era. *Nature Review Genetics, 12*, 640–653.
-