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Article

Twin Registries Moving Forward and Meeting the Future: A Review

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Abstract

Twin registries have developed as a valuable resource for the study of many aspects of disease and society over the years in many different countries. A number of these registries include large numbers of twins with data collected at varying information levels for twin cohorts over the past several decades. More recent expansion of twin datasets has allowed for the collection of genetic data, together with many other levels of 'omic' information along with multiple demographic, physiological, health outcomes and other measures typically used in epidemiologic research. Other twin data sources outside these registries reflect research interests in particular aspects of disease or specific phenotypic assessment. Twin registries have the potential to play a key role in many aspects of the artificial intelligence/machine learning-driven projects of the future and will continue to keep adapting to the changing research landscape.

Keywords: Registries; data; omics; epigenetics; microbiome; artificial intelligence; personalized medicine

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Background to Twin Registries

'Mr Jones's Case of Twins' (Jones, 1811) documented the earliest published article on twins in 1811 with the unexpected finding of a second fetus following labor and discussions on whether birth of the second twin child should be left and trusted to 'nature'. While much of the literature for the following 60 years would center on obstetric considerations, it was not until Francis Galton's study in 1875 when he recognized the potential of assessing shared environment and genetic differences through the study of twins. He made use of these findings in developing the first twin psychological questionnaire to query behavioral tendencies (Burbridge, 2001). Since then, the recognition of twins to provide a powerful resource for exploring the role of genes and environment gathered speed through the establishment of twin registries.

The first reported use of twins in a registry was provided as part of the Danish Cancer Registry in 1942 (Busk et al., 1948) documenting 336 twin-pairs, but it was later in 1954 that the Danish Twin Registry was formally established. This national twin register represents the oldest in the world, having grown from the collection of twins born in Denmark from 1870 to 1910 to now having a total of more than 65,000 twin-pairs included in the registry (Skytthe et al., 2013). This was followed by the Connecticut Twin Registry in 1961 (Honeyman, 1961) and then the first mention of a twin registry dedicated to eye research in 1970, with the documented collection of over 650 twins in the Twin Eye Registry in the Washington DC area of the USA, aimed at studying diabetic retinopathy, glaucoma and myopia (Schwartz, 1970). Since then, there has been a growth in twin registries across the globe, with over 30 of these currently listed by the International Society for Twin Studies (http://www.twinstudies.org/information/twinregisters/).

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Approaches to Building Twin Registries

Varied study designs have been used by the different twin registries worldwide. For many twin registries, the initial approach to document twins was through linkage to national health population-based records. This population-based approach has been widely used by the Scandinavian countries when forming the Danish, Swedish, Finnish and Norwegian Twin Registries (Kaprio et al., 1990). Other twin registries such as the Australian Twin Registry (ATR) are twin-volunteer-based and now house records on over 40,000 twin-pairs of all zygosity types and ages unselected for their health or medical history. The ATR facilitates researcher-led investigations rather than undertaking its own research studies (Hopper et al., 2013). These twin registries have allowed for the documentation of changing trends in disease in twins as well as prevalence changes in monozygotic (MZ) and dizygotic (DZ) twins over the years. Other twin registries have arisen through access to veteran affairs data. These include the Vietnam Era Twin Registry, composed of over 7,000 male–male twin-pairs of conscripts who served in the military during the time of the Vietnam conflict (1965–1975; Goldberg et al., 2002) and the The National Academy of Sciences-National Research Council Twin Registry (NAS-NRC Twin Registry) in the USA of 16,000 White male twin-pairs born in the years 1917–1927 who served in the armed forces (Gatz et al., 2015). The above registries used a questionnaire to assess zygosity and health but have since followed up with additional questionnaires on education, employment history and earnings, as well as linkage to data records for mortality, disability and medical data. Other registries such as the Minnesota Twin Registry represent a birth-record-based twin registry, with data going back to 1904 with over 4,000 twins combined with questionnaire data on

personality, occupational interests, demographics and leisure-time activities (Krueger & Johnson, 2002).

Future Proofing Twin Registries

Twin registries provide a repository of information pertaining to twins allowing for qualitative assessment of twins through questionnaires that explore multiple facets of interest to researchers. In addition, they provide quantitative genetic methods to assess zygosity, concordance, correlations and heritability estimates. Investigation of the relative importance of genetic and environmental influences on a phenotype is also achieved through a number of twin designs, including the classical twin study, co-twin control study, within-pair twin family study, longitudinal twin studies, adopted twin study and randomized controlled trials (RCTs).

Through their life span, twin studies are usually designed to longitudinally follow up their participants from the moment of recruitment to older ages. This presents with huge opportunities to study a variety of life-course factors and address public health issues affecting different demographics and age groups. But, as is the case with all longitudinal information, the information housed in twin registries is potentially finite and restricted by normal factors determining continued participation such as attrition and longevity. This, therefore, poses a challenge in having an extremely valuable population or cohort resource at one level but the need to assure its continued use and relevance so that it can be future proofed in a rapidly changing environment. Longitudinal studies on registry twins provide valuable snapshots of information on a twin or twin cohort at varying timepoints in relation to disease phenotype and progression, but they are limited to questionnaires and standard twin statistics unless additional levels of data are available. Twin registries have established and collected other levels of information that can be used in the future, long after the normal life expectancy of their participants. These sources of information include several 'omics' data to enhance understanding of disease and extend this to complex diseases and enable identification of genetic risks, such as DNA genomic information through genome-wide association studies, next-generation sequencing, as well as explore other mechanisms of genetic changes such as gene expression regulation or various non-sequence-related epigenetic modifications (Kaminsky et al., 2009; Pedersen et al., 2002; Skytthe et al., 2006, 2013; Spector & Williams, 2006). Some twin registries such as Twins UK have extended beyond the collection of only a genetic sample to also include microbiome and biochemical data, some of which will be described in more detail below. These broad sample collections will ultimately allow for investigation of extensive clinical, genetic, physiological, behavioral and lifestyle data to provide a holistic approach to investigation of common diseases (Moayyeri et al., 2013). The ability to undertake such studies comes from access to a range of tissue samples, including DNA, cell lines, serum, plasma, stool, urine, fat and skin, collected over multiple time points to provide the most comprehensive representation of an individual as possible.

Twin Studies in Epigenetics

In no other field of genetic research are natural twin experiments more relevant than in epigenetics. Methylation of a cytosine residue serves as a molecular interface with heritable, sequence variants of the DNA, which allows for environmental influences to alter transcription. Previous twin studies have demonstrated that population-wide variability of differentially methylated cytosine paired with guanidine (CpG) represents sites most readily affected by nonshared environmental exposures. This compares to one-third of the methylation variance determined by genetic additive effects (Busche et al., 2015) that in addition to changes in DNA sequence can also affect the estimation of differentially methylated positions in the genome (Dyke et al., 2015).

Epigenetic diversity arises throughout life, being reflected in differences in environmental exposures at early intrauterine life (Gordon et al., 2011), growth during life course from childhood (Martino et al., 2013) and through later life (Fraga et al., 2005). Therefore, differential methylation patterns over a person's life can potentially explain larger proportions of phenotypic variability than DNA variants (Liang et al., 2015). Additionally, preexisting differential methylation inherited from parents/grandparents can also determine the patterns of subsequent interactions between an individual and environment (Klengel & Binder, 2015; Klengel et al., 2013). Thus, disentangling genetic from epigenetic marker effects of shared or nonshared environmental factors in epigenome-wide association studies (EWAS) is not a trivial exercise and presents a challenge even in well-powered large datasets that are currently generated through high-throughput platforms.

The Discordant MZ Twin Model

The discordant MZ twin model is a modern-day extension of the co-twin control methodology, first described in the early 20th century (Gesell, 1942). The purpose is to have a matched pairwise comparison between the epigenetic status and degree of phenotypic dissimilarity or discordance. MZ twins largely share the same genotypes and transgenerational epigenetic events (Wang et al., 2014) from perinatal exposure onward (Gordon et al., 2012; Kaati et al., 2002) that typically determines subsequent and stable patterns of gene expression profiles through the process of developmental epigenetic programming (Hochberg et al., 2011). For example, it is known that parental imprinting is modulated through epigenetic changes and is widespread across the genome (Baran et al., 2015; Zink et al., 2018) with subsequent strong effect on health and disease (Begemann et al., 2018). Epigenetic investigations in phenotypically discordant MZ twins have been able to show that aberrant imprinting in Beckwith–Wiedemann syndrome (Weksberg et al., 2002), Silver–Russell syndrome (Riess et al., 2016) and others can exist.

Theoretical models show that the MZ power of discordant twin designs, compared to traditional unstructured cross-sectional regression-based models, rises proportionally with higher estimates of genetic heritability of the phenotypic traits (Li et al., 2018). This is apparent even after discounting for the presence of other confounders that are common in most diseases of complex etiology, such as demographic factors and life-course environmental exposures. MZ twin discordance models effectively remove the effect of most shared prenatal and early childhood heritable factors or exposures that are inherently difficult to model statistically. They also indirectly mitigate the impact of other confounding factors, such as those related to varied cell composition of sampled tissues included in EWAS analysis, thereby improving the uniformity of adjustment and performance of various deconvolution methods (Teschendorff & Zheng, 2017).

Despite the improving availability of epigenetic information from large population-based unrelated-sample cohorts (whose results are being catalogued and curated in several repositories; Li, Zou et al., 2019; Liu et al., 2019), the discordant MZ twin model

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remains very popular (Table 1). Taking advantage of the additional power from this type of study design, important associations between differential methylation and several common traits, such as age-related macular degeneration (Wei et al., 2012), rheumatoid arthritis (Svendsen et al., 2016; Webster et al., 2018), psychiatric (Chen et al., 2018; Córdova-Palomera et al., 2018; Kesselmeier et al., 2018; Peng et al., 2018), metabolic phenotypes (Li, Zhang et al., 2019; Peng et al., 2019) and others have been reported in the literature (Table 1). This trend is likely to continue in the short term, given the additional accuracy and increased popularity of pyrosequencing-based approaches when comparing the performance of multiple DNA methylation methods between different cell types (Blueprint Consortium, 2016), although the technology remains comparatively expensive.

The Human Microbiome

The human microbiota consists of up to 100 trillion living cells (Turnbaugh et al., 2007), a much higher number compared to the 37 trillion cells that make up the human body (Bianconi et al., 2013). At over 3 million unique genes (Qin et al., 2010), the genetic complexity of the human microbiome is orders of magnitude higher than that of humans' few tens of thousands (Salzberg, 2018). These permanent inhabitants of the human body appear to play critical roles in both normal human (Le Chatelier et al., 2013) and xenobiotic metabolism (Zimmermann et al., 2019) and may have profound effects over human health (Gilbert et al., 2016). The human microbiota represents another layer of complexity in the quest to better understand mechanisms that contribute to our physiological homeostatic equilibria, and significant efforts are therefore being dedicated to research the interactions between host and microbiome.

Studies of host genetic mechanisms controlling the abundance and diversity of the microbiota have provided a very nuanced picture. While earlier studies conducted on small sample sizes of 20–30 twin-pairs suggested that correlation between microbiomes was highest among MZ compared with DZ twins or unrelated individuals (Stewart et al., 2005), a subsequent twin study using 16S ribosomal RNA metagenomic sequencing found no evidence in favor of heritability of the microbiota diversity (as measured by uniFrac, a commonly used metric of ecological diversity; Lozupone et al., 2006). Subsequent studies of the human microbiota, based on deep metagenomic pyrosequencing of 16S rRNA genes, have revealed that the majority of the metagenomic information is currently not mapped to specific reference genomes of known bacterial species (Turnbaugh et al., 2010). This can affect our ability to estimate the diversity of the microbiota in humans and make reliable comparisons difficult between twin and unrelated subjects. In addition, the amount of the microbiome complexity observed was directly dependent on the depth of the sequencing information (Turnbaugh et al., 2010).

Higher powered classic twin models have subsequently improved the estimates of the heritable component of the human microbiome. Using data from 416 twin-pairs, Goodrich et al. (2014) concluded that while there is little support for genetic control over microbiome diversity in humans, there was substantial heritability for the numbers and abundance of operational taxonomic units (OTUs), the individual components of the microbiome in the gut. Consistent suggestions that coverage and statistical power affect microbiome heritability estimates were confirmed in a subsequent and improved classic twin model experiment involving 1,126 MZ and DZ twin-pairs, which provided increased estimates of heritability across all the OTUs assessed (Goodrich et al., 2016). The authors also found association between OTU presence and genes that contribute to olfaction and diet (Goodrich et al., 2016). Surprisingly, the gut microbiome preserves a degree of stability over decades of life, since the genetic variability appears to be more similar among MZ twins, even at older ages (Xie et al., 2016).

Although there is a better understanding of the genetic component determining diversity and composition of the human microbiome, several questions remain open. For example, the true nature of the interaction between the host genome and the microbiome remains unknown. Dietary preferences are heritable (Teucher et al., 2007) and can also directly cause changes in the gut microbiome (Cotillard et al., 2013; Shoaie et al., 2015). It is also unclear whether, and to what extent, innate (Huang, 2015; Thaiss et al., 2016; Yu et al., 2019) and adaptive immunity (Bonder et al., 2016) can affect the microbiome ecology. It is likely, however, that this is a two-way process (Slack et al., 2009), as the microbiome can induce immunological systemic changes, affecting organs and systems away from the gut (Erny et al., 2015). Finally, the ways in which the gut microbial ecology interacts with the microbiome are complex and need to be better understood. While dietary and host metabolic factors certainly influence the gut microbiome (Shoaie et al., 2015), numerous products of human metabolism are processed in the human gut by the microbial flora (Tremaroli & Backhed, 2012), which may interfere with the systemic wellbeing and therefore influence disease causation.

Twin Registries and Randomised Control Trials (RCTs)

Every clinical intervention is routinely assessed through RCTs that need to evaluate the efficacy of the intervention and its safety. RCTs need to be sufficiently well powered to capture the clinical and demographic complexities of the targeted population, which needs to be balanced against the time and material costs involved in running them. A very large clinical trial, in addition to the costs related to study setup and patient monitoring, may unduly delay the availability of potentially life-saving medication to the needing patients. Matching and randomization across the two arms of RCTs is critical to avoid bias in assessing the outcomes and allows a more realistic evaluation of cost-effectiveness of the treatment. The co-MZ twin model, due to its massive bias-reducing matching potential, is again thought to provide an ideal setting for RCTs (Plomin & Haworth, 2010).

Experience has shown that this path, despite its theoretical potential, remains relatively unexplored, presumably due to lack of availability of twin siblings (Sumathipala et al., 2018). In addition, twins participating in RCTs tend to be assigned to the same intervention arm (Sumathipala et al., 2018), which may be a reflection of the genetically determined tendency toward phenotypic concordance in MZ twins, or due to a general preference toward being treated the same (Bernardo et al., 2015), perhaps due to parental preferences or psychological reasons ingrained in the participants' twin identity.

Given the expected relatively low numbers of disease-discordant MZ twins available for therapies targeting rarer conditions, a more realistic option is to encourage participation of twins, MZ pairs in particular, to larger RCTs evaluating efficacy of large-scale public health interventions where assignment to any treatment arm is not constrained by the presence of a disease and where side effects will be reasonably negligible. For instance, several past and ongoing studies that continue to assess the efficacy of increased intake of antioxidants against arthritis (Canter et al., 2007), cardiovascular disease (Ashor et al., 2015) and others would be well-suited instances where twin participation in opposing intervention arms could add

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Table 1. List of epigenetic studies that have used the discordant MZ twin model in the past five years

Author	Year	PMID	MZ sample	Method	Trait
Peng et al.	2019	31031806	69	Bisulfite pyrosequencing	Glucose metabolism
Souren et al.	2019	31064978	45	Illumina Infinium MethylationEPIC BeadChip assay	Multiple sclerosis
Ramos et al.	2019	30947741	27	Illumina Infinium HumanMethylation450 BeadChips	Sclerosis
Córdova-Palomera et al.	2018	30458022	17	Illumina Infinium HumanMethylation450 BeadChips	Depression
Mohandas et al.	2019	31166810	15	Illumina Infinium MethylationEPIC BeadChip assay	Epilepsy
Wang et al.	2019	30668190	9	Infinium HumanMethylation27 BeadChip	Hodgkin's Lymphoma
Tarr et al.	2019	31164693	3	Illumina Infinium HumanMethylation450 BeadChips	Amyotrophic lateral sclerosis
Li et al.	2019	31152155	30	Bisulfite pyrosequencing	BMI
Peng et al.	2018	29781947	119	Bisulfite pyrosequencing, 450K BeadChip	Depression
Ulff-Møller et al.	2018	29361205	15	Illumina Infinium HumanMethylation450 BeadChips	Systemic Lupus Erythematosus
Chen et al.	2018	28322272	14	Illumina Infinium HumanMethylation450 BeadChips	Attention-deficit disorder
Jiao et al.	2017	29039597	4	Reduced representation bisulfite sequencing	Cerebral palsy
Kesselmeier et al.	2018	27367046	5	Illumina Infinium HumanMethylation450 BeadChips	Anorexia nervosa
Hwang et al.	2018	30291282	28	Illumina Infinium HumanMethylation450 BeadChips	Diabetes
Webster et al.	2018	30176915	79	Illumina Infinium HumanMethylation450 BeadChips	Rheumatoid arthritis
Casey et al.	2017	28032437	52	Illumina Infinium HumanMethylation450 BeadChip	Birth weight discordance, cortical morphology
Kaut et al.	2017	28081695	12	Illumina Infinium HumanMethylation450 BeadChips	Parkinson's disease
Yuan	2017	29043999	2	methyl-CpG-binding domain proteins (MBD) chromatography, Solexa sequencing	Cerebral palsy
Malki et al.	2016	27300265	97	8.1-K-CpG microarray	Depression
Svendsen et al.	2016	27909437	28	HumanMethylation450	Rheumatoid Arthritis
Pietiläinen et al.	2016	26499446	26	HumanMethylation450 BeadChip	Obesity, BMI
Elboudwarej et al.	2016	26782299	7	Infinium HumanMethylation450 BeadChip array	Diabetes
Oudejans et al.	2016	26870946	2	Bisulfite pyrosequencing	Cardiovascular risk, preeclampsia
van Dongen et al.	2015	26508088	66	Illumina Infinium HumanMethylation450 BeadChip	Aggressive behavior
Murphy et al.	2015	26691723	37	HumanMethylation450 BeadChip array	Asthma
Ollikainen et al.	2015	25866590	30	Illumina Infinium HumanMethylation450 BeadChips	Obersity, fatty liver disease
Bahl et al.	2015	26678050	20	Illumina Infinium HumanMethylation450 BeadChip	Blood changes in response to hormone replacement therapy (HRT)
Allione et al.	2015	26043106	20	Illumina Infinium HumanMethylation450 BeadChips	Smoking habit
Córdova-Palomera et al.	2015	25952135	17	Illumina Infinium HumanMethylation450 BeadChips	Depression
Wong et al.	2015	26678051	15	Illumina Infinium HumanMethylation450 BeadChips	Diurnal rhythm
Riess et al.	2016	26691664	6	methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA)	Silver–Russell syndrome
Castellani et al.	2015	26441003	2	NimbleGen Human DNA Methylation	Schizophrenia

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Table 1. (*Continued*)

Author	Year	PMID	MZ sample	Method	Trait
Lévesque et al.	2014	25437055	37	Illumina Infinium HumanMethylation450 BeadChips	Ageing
Yuan et al.	2014	25502755	27	MeDIP-sequencing	Diabetes
Wolber et al.	2014	25184702	21	Illumina Infinium HumanMethylation450 BeadChips	Hearing loss
Dempster et al.	2014	24929637	18	Illumina Infinium HumanMethylation450 BeadChips	Depression
Stefan et al.	2014	24210274	6	HumanMethylation27 BeadChip	Diabetes
Conroy et al.	2014	24828792	2	Agilent 180K array	Landau–Kleffner syndrome
Wong et al.	2014	23608919	50	Illumina Infinium HumanMethylation450 BeadChips	Autism
Tsai et al.	2015	26563994	71	Illumina Infinium HumanMethylation450 BeadChips	Birth weight

BMI, body mass index.

power and improve the assessment of the true benefits of the intervention. Future clinical trials will, and should be able to, take advantage of the growing number of twin registries and the documented higher health awareness and willingness to participate in public good health research of the participants in these registries (Johnsson et al., 2010).

Non-twin Registry Resources

While twin registries provide opportunities for excellent epidemiological studies, it is clear that many other studies involving twins exist outside such registries and these also play an important and key role in clinical research. These studies may involve twins typically ascertained during the course of an ongoing study into a particular disease and thereby captured by in-house registries, studies that are seeking individuals of both a sporadic and familial nature, or through acquisition of twins for a specific task. In terms of family studies, these can range from collection of sib pairs/twins through collection of multiaffected individuals in a single generation through to affected members from multigenerational families. Reflecting recruitment, such family members may be given one or multiple psychological or health or lifestyle questionnaires providing medical history, as well as clinical examination and multiple imaging modalities to capture information of the organ/tissue of interest. Additionally, multiple samples will typically be obtained ranging from DNA/RNA, plasma, serum, saliva, blood, skin, microbiome and biochemical specimens that fall under the given human research ethics for the study. While numbers of recruited twins may not be large compared to twin registries, they do tend to provide highly targeted and perhaps extreme examples of clinical interests such as partial or total disease concordance, differences in biochemical or microbiome, genetic sequence, protein or epigenetic profile within MZ twins. These indicators can provide a wealth of information that may not be clearly visible in a twin registry unless there has been a deep level of phenotype interrogation across multiple traits/diseases within the collected twins.

A recent study – The National Aeronautics and Space Administration (NASA) twin study – is a case in point (Garrett-Bakelman et al., 2019). In that twin study, an MZ twin-pair was compared, consisting of a NASA astronaut who spent a year on the International Space Station and his brother who had remained on Earth. Multiple lines of research were undertaken, including physiological, telomeric, transcriptomic, epigenetic, proteomic, metabolomic, immune, microbiomic, cardiovascular, vision-related and cognitive. Measures were collected over 25 months prior, during and post return from the mission with the aim of elucidating changes in biological measures over extended time periods in space. While a number of initial changes were noted such as a lengthening of telomeres, gene regulation (epigenetic and transcriptional data), gut microbiome composition, body weight, carotid artery dimensions, subfoveal choroidal thickness and peripapillary total retinal thickness, and serum metabolites, most of these measures rapidly returned to preflight levels on return to Earth. However, the greatest change was noted for a series of 'space genes' where significant gene expression changes were still disrupted after 6 months return to Earth. These involved hypoxia, mitochondrial stress, telomere length, DNA damage, DNA repair, collagen, blood clotting, bone formation and hyperactive immune activity gene pathways, as well as increased DNA damage, increased numbers of short telomeres and attenuated cognitive function (Garrett-Bakelman et al., 2019).

Looking Into the Future: Twin Registries in the Personalized Medicine Era

There is an ever-increasing desire from researchers for increased amounts of data from a diverse variety of sources from twins. These demands for data will continue to evolve, especially given the intersection of artificial intelligence, machine learning algorithms and availability of big data. As such, twin registries will have to continually evolve with these demands. For instance, the recent PREDICT 1 Study investigated personal metabolomics in response to food using a multiomics approach in over 1,000 twins and singletons from the UK and USA (Berry et al., 2019). This study took measures on glycemic, insulinemic and lipemic postprandial responses combined with genetic, metabolic, metagenomics and meal-context contributions to postprandial responses and involved the use of 110 MZ and 25 DZ twin-pairs in interim analysis of genetic contributions. These findings were further integrated with metabolic burden and gut microbiome to predict how an individual would respond to food. The sources of data and outcomes were then assessed through the use of machine-learning algorithms to indicate that 46% of overall variation in glycemic responses could be predicted from meal content and baseline characteristics rather than genetic and microbiome factors. Such findings advance our understanding that there is growing

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evidence to indicate that the use of personalized nutritional guidelines rather than a population-based approach may be the most appropriate route for guiding individual health.

Conclusions

Twin registries worldwide are becoming more aware of the unique contributions that they can offer in many different research areas and are increasing efforts to improve their collaborative efforts (Ferreira et al., 2016). Different twin registry models exist, with one extreme being that of the research-intensive twin registry such as Twins UK where research is typically driven from within. The opposite end of the scale is that of the more classic registry such as the ATR where information on twins is housed, and the registry provides the gateway to researchers wanting to access twins for their own studies following internal ethics approval. Currently, both of these registry approaches appear to work within their own national remits, but twin repositories rely on continued funding for their ongoing success and therefore can be influenced by other external factors and therefore need to remain relevant within society. Twin studies still have a unique part to play in advancing our understanding of disease or health and typically present at the forefront of many studies in exploring the intertwining of microbiologic factors with genetic, epigenetic, metabolic, physiological, biochemical and immune functions that are needed to maintain a good homeostasis. In the future, it is likely that the vast amounts of data available on twins combined with advances in artificial intelligence/machine learning will provide many research findings and pave the way for studies in wider sections of the community.

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