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The European Disorder of Sex Development Registry: A Virtual Research Environment

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Abstract
Disorders of sex development (DSD) are a rare group of conditions which require further research. Effective research into understanding the aetiology, as well as long-term outcome of these rare conditions, requires multicentre collaboration often across national boundaries. The EU-funded EuroDSD programme (www.eurodsd.eu) is one such collaboration involving clinical centres and clinical and genetic experts across Europe. At the heart of the EuroDSD collaboration is a European DSD registry and a targeted virtual research environment (VRE) that supports the sharing of DSD data. Security, ethics and information governance are cornerstones of this infrastructure. This paper describes the infrastructure that has been developed, the inherent challenges in security, availability and dependability that must be overcome for the enterprise to succeed and provides a sample of the data that are stored in the registry along with a summary analysis of the current data sets.

Suspected cases of a disorder of sex development (DSD) are usually present in early infancy with a variable abnormality of the development of the external and/or internal reproductive organs. There is a large amount of variation in how these patients are managed across the world. In addition, there are enormous gaps in our knowledge about the aetiology of these conditions and the long-term outcome in affected adults. The management of these patients requires multidisciplinary input, and, increasingly, this service is being delivered through organised clinical networks which rely on research as a means of auditing and improving their service.

The Consensus Workshop on DSD which was jointly hosted by the European Society of Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society of North America stressed the need for the creation and maintenance of a database in centres of expertise [Hughes et al., 2006]. Such databases do exist in many regional and national centres and have provided valuable insight into many aspects of DSD, including epidemiology [Ahmed et al., 2004], aetiology [Ahmed et al., 2000a; Gottlieb et al., 2004], variation of disease expression [Bebermeier et al., 2006], initial adjustment of parents to their affected child's condition [Duguid et al., 2007], and long-term outcome [Lux et al., 2009]. However, these databases and registers lack international uniformity and have not been integrated – a key feature particularly desirable when dealing with a rare group of conditions. With the initial help of ESPE and, more recently, from the European Union, a European web-based register and research environment for DSD has now been in operation for approximately 2 years. This infrastructure is currently helping the EuroDSD programme (www.eurodsd.com)

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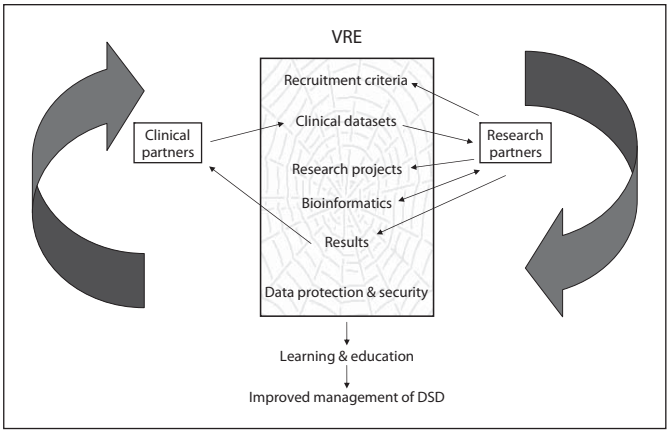

Fig. 1. The central role of the European DSD registry as the platform used for exchange of all information between the clinical and research partners with targeted tools supporting a VRE. Clinical partners enter data into the registry. Research partners subsequently design studies, assign recruitment criteria and search the registry for suitable cases. Research partners contact clinical partners for further details of positive cases, perform studies and enter data into the VRE so that new studies can be designed and knowledge promulgated.

and has the potential to address many unanswered questions in the future.

This paper describes the construction of the current EuroDSD registry, the operating procedures, general description of the data that are held within the registry, and the future direction of the registry as it develops into a complete virtual research environment (VRE) for research into DSD.

The Creation of the Registry

The cornerstones of the European DSD registry model are site autonomy and the detailed definition and enforcement of standard operating procedures on access, usage and contribution of data to the registry. Details of the standard operating procedures are available at https://tethys.nesc.gla.ac.uk. Each clinical site is solely responsible for deciding what datasets it can share, with which partner sites and in what context. To support this, the design of the registry has been driven by security, incorporating both the needs of the clinical community and ethical oversight required on information governance. The registry provides various functionality including querying, uploading/edit/deletion of DSD cases and cross-searching of cases. The greatest challenge to date related to data heterogeneity, software and data storage heterogeneity and language heterogeneity has been overcome by developing a consensus around a core data model which is largely based on the revised DSD nomenclature [Lux et al., 2009]. The registry platform allows data entry of sequential clinical examinations and development of specific modules, such as a genetic module which records details of method and results of genetic analyses, the mutations that may have been found and the methods of analysis used.

The development of the registry and associated VRE draws heavily on e-Science tools and expertise in information security at the National e-Science Centre (NeSC) at the University of Glasgow (www.nesc.ac.uk). This VRE provides an extensible and personalisable framework that integrates applications, services and resources targeted to the specific-research needs of the DSD clinical and research collaborators. Successful VREs allow aspects of distribution of resources and heterogeneity of data to be made seamless and transparent, targeted to the needs and roles of the scientists. VREs ensure that the data can only be accessed by those with sufficient privileges. A variety of security-supporting portal-based tools [Sinnott et al., 2007] and advanced authorisation solutions [Sinnott et al., 2008] have been utilized for this purpose. User and institute-oriented access control is achieved through the Internet2 Shibboleth technologies (http://shibboleth.internet2.edu) which supports federated access control and delivery of digitally signed X509-based attribute certificates. These are used for automatic configuration of portal contents, e.g. for restriction of access and usage of associated datasets according to the assigned user role within the portal. Figure 1 shows how the registry is central to the EuroDSD research programme and how it acts as a key component of the VRE where clinical data and research results are deposited securely and shared by centres across Europe with appropriate privileges to develop and design new studies.

Registry Users and Their Roles

The European DSD Registry has a panel that consists of members of the ESPE DSD Group (www.eurospe.org/about/workinggroups/DSD.html). Prospective users are expected to complete a simple online-application form to apply to this panel for approval. There are 2 broad categories of users of the registry: clinical partners and research partners.

Clinical partners are eligible to enter data into the registry. Only full members of a national or international clinical professional society are allowed to become a clinical partner and need to show proof of membership. To ensure maximum levels of governance of clinical data, applications from more than one clinical partner from the same institution is discouraged. Each clinical partner can identify other members of their team who will require access and act as local data contributor. Thus, the clinical partner will remain responsible and accountable for data entry. The level of data sharing is configurable and can be done at a local level, a national level, a EuroDSD level, or a wider international level as deemed appropriate by the clinical collaborator. Thus, non-EuroDSD members are able to use the registry to add their own data and use it as a local store. In this case, these data sets are not accessible to other partners or EuroDSD members. The clinical partner is responsible for provision of information to the patient and obtaining consent.

Currently, the research partners within the EuroDSD consortium are the only research partners. It is envisaged that after the lifetime of the EUFP7-funded EuroDSD programme new research partners shall be able to apply to the ESPE DSD registry panel with brief details of their proposed study and search criteria. Research partners are required to demonstrate that they have obtained ethics approval for their respective studies. The panel shall be able to indicate the number of cases that fulfil the recruitment criteria of the investigator's studies and, for a fixed fee, provide contact details of the clinical partner responsible for the cases.

Some partners may have joint clinical and research partner status. These partners need to continue renewing their research partner status.

Eligibility of Cases in Registry

Any adult or child with a DSD at a centre with an approved clinician is eligible to be included in the EuroDSD registry. Participating cases and their legal guardians (if patients are less than 16 years old) are approached by the clinical partner or a member of their team for approval to include the details on the registry. It should be emphasised that the registry only contains non-identifiable data and although there may be no need to obtain informed consent in some countries such as the UK to share such data with European Economic Area (EEA) members, which includes the 27 countries of the EU and the 3 countries of Norway, Iceland and Liechtenstein, it is recognised that some countries within the EEA, as well as outwith Europe, may have different national regulations which require opt-in consent models. For uniformity as well as for compliance with the feedback received from patient and user support groups, the opt-in system is the recommended standard of consent. As the registry includes children, an information sheet has been created for those under the age of 14 years. Over the age of 14 years, these young adults can be provided with the adult information sheet. Minors (under 16 years) may only participate if both, the minor and a parent or legal guardian, do not raise any objections. If the minor lacks the capacity to provide assent, parent or legal guardian permission is sufficient. On turning 16 years old, the registry will automatically remind the clinical partner to send the participant an adult information sheet. At any time, a participant may request that his or her data or their child's data no longer be made available in the registry. Participants can make this request to their local clinician who is the clinical partner and who will inform the panel. The participant can also make this request directly to the panel. A confirmation of withdrawal shall be sent to the clinical partner.

The current European DSD registry has been approved by the local Caldicott Guardian in Glasgow, by the UK Research Ethics Committee and the Ethics Committee of the EuroDSD programme. The Congenital Adrenal Hyperplasia support group and the Androgen Insensitivity Support Group in the UK have also been consulted on the development of the registry. All information stored in the registry, and access to that information, conforms to the UK Data Protection Act (1998). However, all participating clinical partners and research partners are encouraged to follow their own national regulations and provide assurance to the registry panel that national regulations are being followed for data handling as well as research. Generic information sheets and consent forms have been developed and are available at https://tethys.nesc.gla.ac.uk/. The information sheets can be adapted to include the name of the local clinical partner, local institution and local institutional contact.

Data Flow and Security

Figure 2 summarises how information flows in the European DSD registry as well as the security checks that are supported. Audit tracking software monitors access patterns, machine locations and user access more generally. With this information, it is possible to accurately track

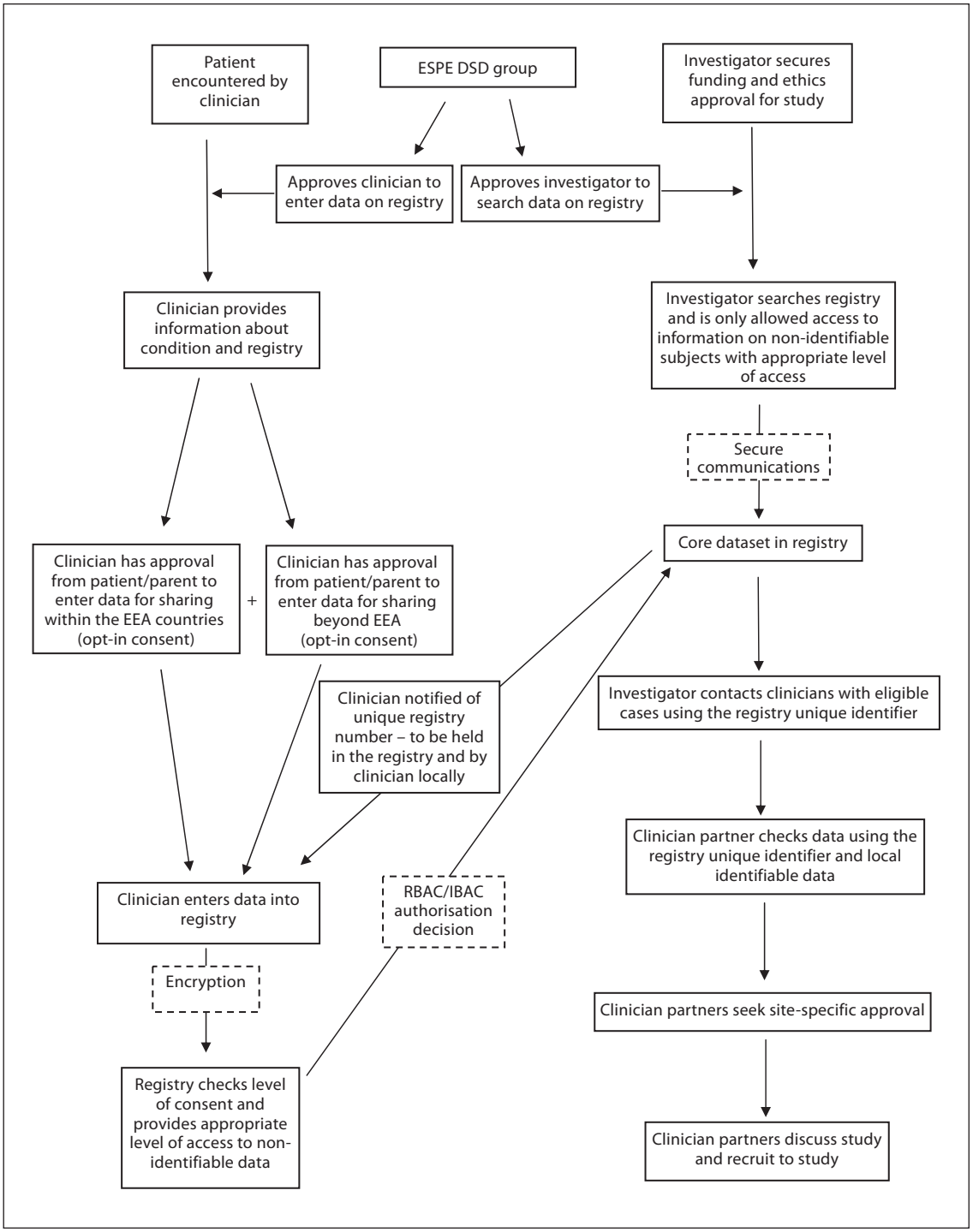

Fig. 2. Data flow within the European DSD registry. EEA = European Economic Area; IBAC = Identity Based Access Control; RBAC = Role Based Access Control.

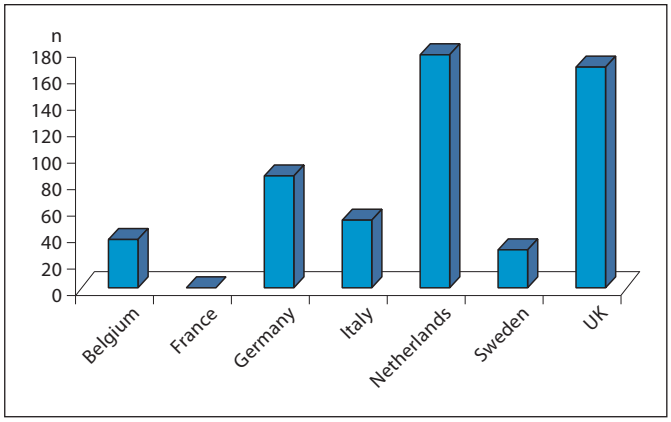

Fig. 3. Distribution of cases according to country (February 2010).

and identify both legitimate and any potential illegal access attempts – this is achieved in part through tools provided by Google Analytics. The VRE and registry are themselves hosted in a portal that is protected through a targeted Shibboleth Identity Provider (IdP) at the NeSC. In addition to supporting Single Sign-On (SSO) authentication, the IdP also provides digitally signed attribute certificates which are subsequently used to restrict access to and use of data resources available through the portal itself. Assignment of these privileges is made as part of the panel evaluation. Current roles supported include for local contributors only, for EuroDSD contributors, for EuroDSD investigators and for EuroDSD research collaborators. A user not in possession of any of these roles will not be able to access any data resources within the portal.

The registry itself does not include any identifying information on patients directly. Instead, every participant on the registry is assigned a unique identifier generated automatically following entry of a case into the registry. This identifier needs to be kept and associated with local records at the contributing partner site. A record in the registry may also have a local identifier which is kept by the clinical partner, physically and electronically, separately to the registry. The unique identifier contains no identifying information within it. This unique identifier is used to track all information about the participant in the registry. The only way for research partners to find out more about the participants in the registry is to contact the clinical partners whose details shall be linked to the unique identifier. The complete research staff at the NeSC maintains up-to-date training in protection of data on human subjects as detailed at https://tethys.nesc.gla.ac.uk/.

Table 1. Distribution of 548 cases in the European DSD registry by disorder and actual diagnosis

Diagnosis	n
Disorder of gonadal development	137
Partial gonadal dysgenesis	71
Complete gonadal dysgenesis	50
Testicular DSD	6
Ovotesticular DSD	5
Gonadal regression	3
Other	2
Disorder of androgen synthesis	70
17β-HSD deficiency (HSD17B3)	26
P450 oxidoreductase deficiency (POR)	21
5α reductase deficiency (SRD5A2)	15
Combined 17α-hydroxylase/17,20 lyase deficiency	2
Isolated 17,20 lyase deficiency	1
P45O scc deficiency (CYP11A1)	1
Other	4
Disorder of androgen excess	89
21α hydroxylase deficiency (CYP21A)	87
11β hydroxylase deficiency (CYP11B1)	1
Other	1
Disorder of androgen action	186
Complete androgen insensitivity syndrome	144
Partial androgen insensitivity syndrome	40
Other	2
Nonspecific disorder of undermasculinisation	37
Complex anomalies	11
EMS of less than 5	5
EMS of greater than 8	2
EMS between 5 and 8	2
Isolated bilateral cryptorchidism	1
Isolated hypospadias	16
Leydig cell defects	4
Persistent Mullerian Duct Syndrome	2
Cloacal anomaly	1
Defects of mullerian development	4
Mayer-Rokitansky-Kuster-Hauser Syndrome	2
Mullerian duct aplasia, renal agenesis/ectopia cervical somite dysplasia (MURCS)	1
Other	1
Other	18

Description of Cases in Registry

At last review (February 2010), there were 548 cases on the register with a variable number of cases from a variety of clinical centres in Europe which are participating in the EuroDSD research programme (fig. 3). The median year of birth of these cases was 1993 (range, 1927–2009) and the age of presentation ranged from less than 1 month to 62 years. Sex assigned was female in 371 (68%) cases and male in the remaining 177 (32%). Out of the 371 cas-

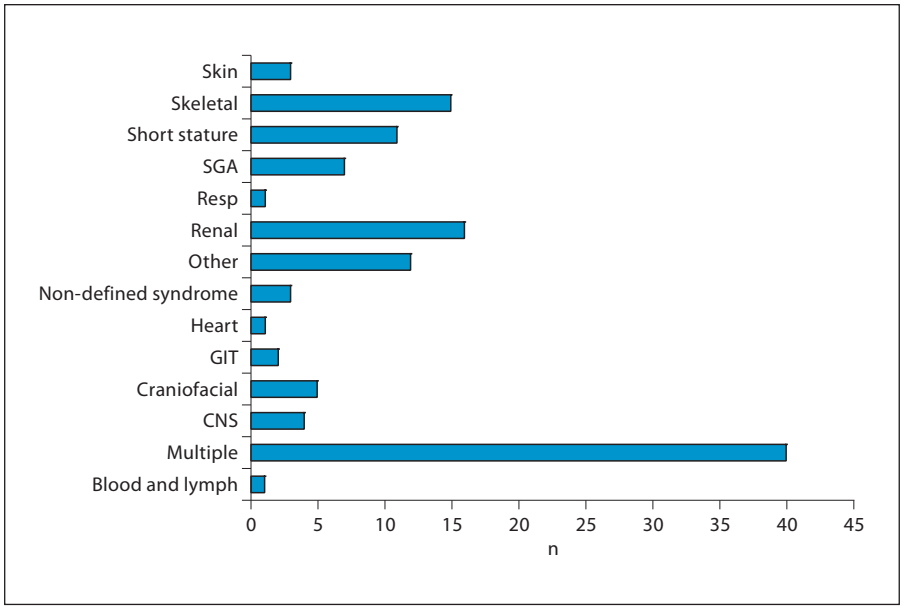

Fig. 4. Associated malformations in cases in registry (February 2010).

es, consent from clinical centre was available to access metadata in 307 cases. Out of these 307 female cases, 229 were 46XY, 58 were 46XX, 8 were 45X/46XY, 2 cases were of complex rearrangements of sex chromosomes and one case was a trisomy of an autosome. Out of the 177 male cases, consent from clinical centre was available to access metadata in 143 cases. Out of these 143 cases, 110 were 46XY, 19 were 45X/46XY, 8 were 46XX and there were 4 cases of another sex chromosome abnormality. The median external masculinisation score (EMS) [Ahmed et al., 2000b] at the first presentation of the cases of 46XY raised as boys and girls was 5.5 (1, 12) and 4 (0, 11), respectively ($p < 0.0001$, Mann Whitney U test). The median EMS at first presentation of the cases of 45X/46XY raised as boys and girls was 5 (2.5, 12) and 4 (0, 10) (NS), respectively.

Amongst the diagnostic criteria based on the revised DSD nomenclature, 'disorders of androgen action' is the commonest disorder type with 186 (34%) cases (table 1). Of these cases, 144 (77%) have been diagnosed as complete androgen insensitivity syndrome, 40 (22%) as partial androgen insensitivity syndrome and 2 (1%) cases have a diagnosis of 'other'. The next most common category is 'disorders of gonadal development' with 137 (25%) cases. Amongst the 548 cases in the registry, a family history of infertility, DSD and parental consanguinity was reported in 45 (8%) cases, 130 (24%) cases and 37 (7%) cases, respectively. In 383 (70%) cases, DNA analysis had already been performed and a DNA abnormality had been detected in 248 (65%) of these 383 cases. Associated malformations are present in 121 (22%) cases, and multiple associated malformations have been reported in a number of cases (fig. 4). Out of the total cohort of 548 cases, a stored sample of DNA was available in 430 cases consented for use within the EuroDSD research programme.

The registry has the ability to perform finer grained search of cases by combining the above fields including search for genetic screens and mutations found, however, this is beyond the scope of this paper.

Summary

In summary, the European DSD registry is a live, security-oriented web-based platform that can act as a resource for research into a number of aspects of DSD. The future direction of the registry is to facilitate the collection of standardised data internationally, thereby, allowing collaborative research to be performed across the globe. The registry has already allowed access for local use to partners from numerous countries (including Argentina, the Czech Republic, Estonia, and Turkey). Its cornerstone is adherence to the highest standards of data security and information governance. The work on this project is still very much ongoing both from a software development and a clinical research/usage perspective. The work has demonstrated that development of advanced VREs is now realistic and moves beyond the

'proof of concept in a software research centre' to production use in a real world clinical and research environment. We continue to work in this space and refine the software solutions to meet a range of criteria deemed important for ethics, information governance and importantly for software guarantees, e.g. on availability. The lessons that have been learnt can be applied to international collaborative research in other rare conditions.

Acknowledgements

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