



Results from a pilot of the Dysmorphology Diagnostic System (DDS)

S Gardner¹, R. Day¹, P Griffiths¹, K Strong¹, C Harrison¹, D Donnai¹, B Kerr¹, K Metcalfe¹, H Brunner², B Dallapiccola³, K Devriendt⁴, M Krajewska-Walasek⁵, N Philip⁶, J Clayton-Smith¹
¹University of Manchester, UK ²UMC St Radboud, Netherlands ³IRCCS – CCS, Italy ⁴KU Leuven, Belgium, ⁵IP-CZD, Poland ⁶Hopitaux de Marseille, France

BACKGROUND

Introduction

- The rarity of dysmorphic conditions means that even in Centres of Expertise, experience may be limited, resulting in delayed or uncertain diagnoses.
- A main aim of the DYSCERNE project (www.dyscerne.org) is to develop an electronic Dysmorphology Diagnostic System (DDS) which will link over 50 European Centres of Expertise in dysmorphology to form a powerful diagnostic tool and educational resource for rare dysmorphic conditions.

DYSCERNE Network

- Comprises 82 clinicians from 76 centres in 30 European countries (fig. 1) with varying levels of expertise in dysmorphology.

DDS Expert Panel

- Comprises the 11 clinicians from the DYSCERNE Partner centres and a further 15 Expert Dysmorphologists, giving a total 26 Expert dysmorphologists from 21 European Centres of Expertise.
- All expert panel members are DYSCERNE Network members.
- There is list of the DDS Expert Panel members on the DYSCERNE website.



Figure 1: The DYSCERNE Network

DDS Workflow

- Submitting Nodes submit patients' clinical information and images via an online submission form.
- An internal review ensures cases are appropriate for the DDS.
- Accepted cases are reviewed by the DDS Expert panel.
- A DYSCERNE Expert Case Report prepared from the consensus of Expert opinions, is sent to the Submitting Node, and includes diagnostic suggestions and recommendations for further investigations or management of the patient.
- Cases with appropriate consent can be stored in the DDS Archive, which will be used to help define and classify new and rare dysmorphic conditions.

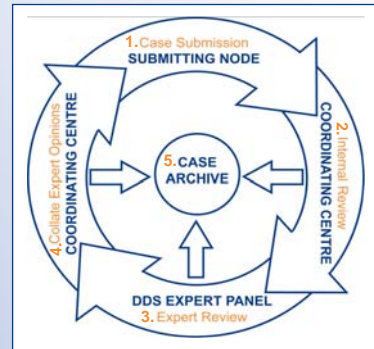


Figure 2: An overview of the DDS workflow

Pilot Structure

- Prior to the full launch of the DDS across the entire DYSCERNE Network, a pilot of the DDS software and work process took place.
- The pilot ran for 4 months and involved 7 Submitting Nodes (Istanbul, Leuven, Manchester, Marseille, Nijmegen, San Giovanni Rotondo & Warsaw,) submitting up to 5 cases each, for review by the entire DDS Expert Panel.

PILOT RESULTS

1. Case Submission

- A total 23 cases were submitted from 6 of the 7 pilot Submitting Nodes.

2. Internal Review

- The internal review outcomes for the 23 submitted cases are shown in table 1.
- Reasons for rejecting cases were: duplicate or incomplete case submissions.
- Reasons for returning a case include: requests for clarification of terms or lab results, missing or inconsistent data or further details required.

Table 1: Internal review outcomes

Outcome	No. of cases (% of total)
Rejected	3 (13.0)
Returned	13 (56.5)
Accepted	7 (30.4)
Total	23 (100)

- All 13 returned cases were resubmitted and subsequently accepted on to the DDS, giving a total of **20 accepted cases** (87% of total cases submitted), an average of 5 cases per month.
- All internal review decisions were made within 5 working days, with 87% of decisions being made within 3 working days.

3. Expert Review

- The average number of reviews per accepted case was 5.4, with 8 cases having 6-10 reviews (fig. 3).
- Discussion forums were opened for 15 of the 20 accepted cases (75%) and the average number of contributors was 3.5.

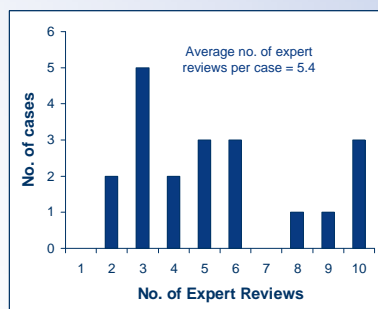


Figure 3: Number of expert reviews/ case

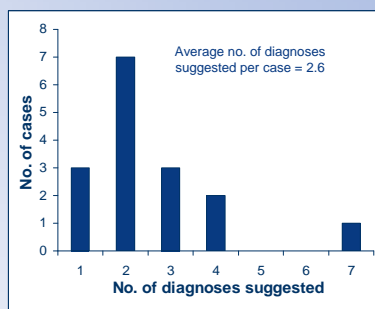


Figure 4: Number of diagnoses suggested/ case

4. DYSCERNE Expert Case Report

- Summary reports were prepared an average of 6 weeks after acceptance, depending on the timing & number of reviews, with 80% completed within 8 weeks.
- 4 cases have been on the DDS for less than 4 weeks and summary reports have not yet been prepared for these.
- For the 16 cases for which summary reports have been prepared:
 - 100% had diagnoses suggested (average of 2.6 diagnoses per case, fig. 4)
 - 100% had further investigations recommended with 15 (94%) cases having either a molecular or cytogenetic test suggested.
 - 100% of cases were described as complex phenotypes with combinations of dysmorphic features, varying congenital abnormalities affecting different body systems and a range of neurocognitive disabilities.
- Feedback on case 1 (table 2) has confirmed the suggested DDS diagnosis at a molecular level.**
- Case 2 (table 2) is a possible new recessive condition worthy of being published as a case report.**

Table 2. Key details of example submitted cases

Case No.	Key words from case details	DDS Diagnostic suggestions	DDS Suggested investigations	Outcome
1	• Hypertelorism • Limb asymmetry • Epilepsy	• Coffin-Lowry syndrome • Robinow syndrome	• DNA for RSK2 analysis • Skeletal survey	• Confirmed RSK2 mutation
2	• Microcephaly • Cleft palate • Hypertelorism • Blepharophimosis • Affected sib pair	• Dubowitz • Cholesterol disorder • Chromosome breakage disorder • DNA repair disorder	• Cholesterol levels • Mitomycin C studies • Array CGH • Metabolic tests	• Suggested submission to journal as a case report
3	• Craniosynostosis • Supernumary nipple • Macrocephaly • GPC3 analysis normal	• Mowat-Wilson syndrome • Simpson-Golabi-Behmel syndrome	• DNA for ZFHX1B analysis	• Pending

Summary

- These results show the DDS is a workable and effective diagnostic system facilitating timely and equitable access for clinicians from across Europe to expert opinions.
- It will increase capacity and accuracy of diagnoses and decrease time from presentation to diagnosis.
- Future audit of the DDS and analysis of the Archive will improve the definition and classification of rare dysmorphic conditions & will promote further clinical research into these complex disorders.
- Moving towards the full launch of the DDS, all 76 proposed Submitting Nodes have been invited to apply for accounts and to date over 50% have done so.

Where can I find out more?

- Our website is at www.dyscerne.org or you can contact:
- Sara Gardner, DDS Network Coordinator, sara.gardner@cmf.nhs.uk, Tel: +44 161 90 17190
- Ruth Day, Clinical Fellow, ruth.day@cmf.nhs.uk, Tel: +44 161 27 64658

