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Design, development and deployment of a web-based interoperable registry for inherited retinal dystrophies in Portugal: the IRD-PT

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Abstract

Background: The development of multicenter patient registries promotes the generation of scientific knowledge by using real-world data. A country-wide, web-based registry for inherited retinal dystrophies (IRDs) empowers patients and community organizations, while supporting formal partnerships research. We aim to describe the design, development and deployment of a country-wide, with investigators and stakeholders in the global aim to develop high-value, high-utility web-based, user-friendly and interoperable registry for IRDs—the IRD-PT.

Results: The IRD-PT is a clinical/genetic research registry included in the *retina.pt* platform (https://www.retina.com. pt), which was developed by the Portuguese Retina Study Group. The *retina.pt* platform collects data on individuals diagnosed with retinal diseases, from several sites across Portugal, with over 1800 participants and over 30,000 consultations to date. The IRD-PT module interacts with the *retina.pt* core system which provides a range of basic functions for patient data management, while the IRD-PT module allows data capture for the specific purpose of IRDs. All IRDs are coded accordingly to the International Statistical Classification of Diseases and Related Health Problems (ICD) 9, ICD 10, ICD 11, and Orphanet Rare Disease Ontology (ORPHA codes) to make the IRD-PT interoperable with other IRD registries across the world. Furthermore, the genes are coded according to the Ontology of Genes and Genomes and Online Mendelian Inheritance in Man, whereas signs and symptoms are coded according to the Human Phenotype Ontology. The IRD-PT module pre-launched at *Centro Hospitalar e Universitário de Coimbra*, the largest reference center for IRDs in Portugal. As of April 1st 2020, finalized data from 537 participants were available for this preliminary analysis.

Conclusions: In the specific field of rare diseases, the use of registries increases research accessibility for individuals, while providing clinicians/investigators with a coherent data ecosystem necessary to boost research. Appropriate design and implementation of patient registries enables rapid decision making and ongoing data mining, ultimately leading to improved patient outcomes. We have described here the principles behind the design, development and deployment of a web-based, user-friendly and interoperable software tool aimed to generate important knowledge and collecting high-quality data on the epidemiology, genomic landscape and natural history of IRDs in Portugal.

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Keywords: Inherited retinal dystrophies, Registry, Rare diseases, Interoperability, Software, Data management, Research, Epidemiology, Natural history, Clinical genetics

Background

The Agency for Healthcare Research and Quality defines a registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" [1]. Clinical registries have existed for decades in the field of ophthalmology [2-5], serving a variety of purposes, which include (1) capturing the epidemiologic features of an ocular disease or condition, (2) tracking outcomes and complications of drugs or procedures, (3) recording adverse events, or (4) combinations of the above [6]. In recent years, policy makers started recognizing clinical registries as an important tool for improving the value of healthcare. Outcome data is now used to fill in gaps of evidence that cannot be provided by randomized controlled trials [6]. Furthermore, data from clinical registries is also increasingly being used to facilitate learning networks and to establish research collaborations between scientific researchers, clinicians, industry, regulators, patient organizations, patients and families [7]. This is especially true for rare diseases where the small number of cases for each disease creates additional barriers in the translational research pathway, and makes identification and establishment of a substantial cohort a very difficult task.

Inherited retinal dystrophies (IRDs) are a clinically and genetically heterogenous group of diseases with an estimated prevalence of 1 in 3000 individuals [8]. Despite some common ground, genetic profiles vary considerably among regions and ethnic groups [9–16], thus highlighting the importance of obtaining reference population-based data. The presence of founder mutations may greatly contribute for these differences, as observed in a large Israeli population [9]. While local hospital-based registries may provide high quality information and resources, their coverage is usually small. To fully understand the prevalence and genomic landscape of IRDs, we must connect knowledge that is widespread throughout miscellaneous registries. The development of multicenter patient registries and natural history studies promote the generation of scientific knowledge by using real-world data. As rare diseases gain visibility as a public health priority and the marketplace expands, acknowledgement of the importance of building collaborative relationships in rare disease research increases [7]. A national, web-based registry for IRDs is able to empower patients and community organizations, while supporting formal partnerships

with investigators and stakeholders in the global aim to

develop high-value, high-utility research. When developing a registry, it is essential to ensure that it is ethically governed, user-friendly and designed with maximum sustainability. This includes the implementation of foundational, structural, semantic, and organizational interoperability processes to optimize the utility of data and allow its linkage to other existing or future registries [7]. By making data computationally accessible, it is possible to bridge compatibility gaps between different hospitals, healthcare systems, registries and languages [17]. Adoption of comprehensive phenotype and rare disease ontologies enables this type of sharing by making data findable, accessible, interoperable, and reusable (FAIR principles) [18]. These features have made Orphanet Rare Disease Ontology (ORDO) a standard for rare disease coding in European health-care systems and led to the widespread adoption of ontologies like the Human Phenotype Ontology (HPO) by global genomics initiatives, like the European Reference Network for Rare Eye Disease (ERN-EYE) [17].

The purpose of this study is to describe the design, development and deployment of a country-wide, webbased, user-friendly and interoperable registry for IRDs—the IRD-PT.

Results

Data capture

The IRD-PT was designed to capture longitudinal data on IRDs. The data captured by the IRD-PT module is kept to a minimum to deliver an efficient and user-friendly data collecting tool. The user must complete all the mandatory fields/check all the mandatory boxes in order to save the entry. However, the system allows editing and/or completion of previously unanswered non-mandatory fields at the user's convenience. The list of covered clinical diagnoses is shown on Table 1, while the list of the genes and their respective Ontology of Genes and Genomes (OGG) and Mendelian Inheritance in Man (MIM) numbers are shown on Table 2. Even though inherited optic neuropathies and other genetically-associated retinal diseases (such as Pseudoxanthoma Elasticum-associated retinopathy or isolated foveal hypoplasia) are not IRDs per se, we opted to include them in the registry since these are common diagnoses in an Ophthalmic Genetics clinic. This is

Table 1 List and ORPHA numbers of the clinical diagnoses covered by the IRD-PT module

	Inherited retinal dystrophies ^a	
	ORPHA 71862	
1. ISOLATED PROGRESSIVE INHERITED RETI- NAL DISORDER (ORPHA 519306)	3. SYNDROMIC INHERITED RETINAL DISOR- DER (ORPHA 519325)	5. CHORIORETINAL DYSTROPHIES (ORPHA 519,300)
1.1 Retinitis punctata albescens (ORPHA 52427)	3.1. Alström syndrome (ORPHA 64)	5.1. Bietti crystalline dystrophy (ORPHA 41751)
1.2. ARB (ORPHA 139455)	3.2. Jalili syndrome (ORPHA 1873)	5.2. CACD (ORPHA 75377)
1.3. Cone/cone-rod dystrophy (ORPHA 1872)	3.3. Senior-Loken syndrome (ORPHA 3156)	5.3. Choroideremia (ORPHA 180)
1.4. Late-onset retinal degeneration (ORPHA 67042)	3.4. Joubert syndrome (ORPHA 475)	5.4. Gyrate atrophy of choroid and retina (ORPHA 414)
1.5. Leber congenital amaurosis (ORPHA 65)	3.5. Usher syndrome (ORPHA 886)	5.5. Helicoid peripapillary chorioretinal degenera- tion (ORPHA 86813)
1.6. Retinitis Pigmentosa AR (ORPHA 791)	3.6. Bardet-Biedl syndrome (ORPHA 110)	5.6. Pigmented paravenous retinochoroidal atro- phy (ORPHA 251295)
1.7. Retinitis Pigmentosa AD (ORPHA 791)	3.7. Hallervorden-Spatz syndrome (ORPHA 157850)	6. HEREDITARY OPTIC NEUROPATHY (ORPHA 98671)
1.8. Retinitis pigmentosa XL (ORPHA 791)	3.8. Syndromic retinitis pigmentosa—other (ORPHA 519325)	6.1. Autosomal dominant optical atrophy (ORPHA 98672)
1.9. Isolated macular dystrophy (ORPHA 519302)	3.9. Kearns-Sayre syndrome (ORPHA 480)	6.2. Leber hereditary optic atrophy (ORPHA 104)
1.9.1. Sorsby fundus dystrophy (59181)	3.10. PXE (ORPHA 758)	6.3. Hereditary optic neuropathy—other (98671)
1.9.2. Stargardt disease (ORPHA 827)	3.11. Alport Syndrome (ORPHA 63)	
1.9.3. Best vitelliform macular dystrophy (ORPHA 1243)	3.12. MIDD (ORPHA 225)	7. OTHER RARE DISORDERS OF THE POSTE- RIOR SEGMENT OF THE EYE (ORPHA 519311)
1.9.4. North Carolina macular dystrophy (ORPHA 75327)	3.13. Cuticular drusen/C3 Glomerulopathy (ORPHA 329918)	7.1. Foveal hypoplasia (ORPHA 519398)
1.10. Pattern dystrophy (ORPHA 63454)	4. INHERITED VITREOUS DYSTROPHIES (ORPHA 519304)	7.2. Coloboma (ORPHA 98942)
1.10.1. Butterfly-shaped pigment dystrophy (ORPHA 99001)	4.1. X-linked retinoschisis (ORPHA 792)	7.3. Ocular albinism (ORPHA 284804)
1.10.2. MFD simulating fundus flavimaculatus (ORPHA 99003)	4.2. Stickler syndrome (ORPHA 828)	7.4. Oculocutaneous albinism (ORPHA 55)
1.10.3. Reticular dystrophy of the RPE (ORPHA 99002)	4.3. Wagner disease (ORPHA 898)	7.5. Other
1.10.4. AOFVD (ORPHA 99000)	4.4. FFEVR (OPRHA 891)	
2. ISOLATED STATIONARY INHERITED RETI- NAL DISORDER (ORPHA 519319)	4.5. Goldmann-Favre syndrome/ESCS	
2.1. Achromatopsia (ORPHA 49382)	4.6. ADVIRC (ORPHA 3086)	
2.2. CSNB (ORPHA 215)		
2.3. Fundus albipunctatus (ORPHA 227796)		
2.4. Familial drusen/Malattia leventinese (ORPHA 75376)		

Bold corresponds to items (groups of diseases) that have dependences

MFD multifocal pattern dystrophy, *AOFVD* adult-onset foveomacular vitelliform dystrophy, *CSNB* congenital stationary night blindness, *PXE* pseudoxanthoma elasticum, *MIDD* maternally-inherited diabetes and deafness, *FEVR* familial exudative vitreoretinopathy, *ADVIRC* autosomal-dominant vitreoretinochoroidopathy, *CACD* central areolar choroidal dystrophy

^a The platform allows the selection of more than one diagnosis

not something previously unseen. In fact, these diseases are also part of the Inherited Retinal Disease Classification proposed by Stone et al. [16].

We were able to design an interoperable module by reusing the *retina.pt* core data elements where appropriate (epidemiological data such as sex, date of birth and patient ID), whilst also incorporating bespoke data elements, sections and forms for the specific field of IRDs (Table 3). Upon selection of a particular item (clinical diagnosis, signs and symptoms, syndromic features, gene or additional diagnoses), a hyperlink is available to direct the user to the correspondent ontology webpage (ORPHA, HPO, OGG).

Table 2 List of available IRD genes^a and their respective Ontology of Genes and Genomes (OGG) and Mendelian Inheritance in Man (MIM) numbers

APCAA OGG3000000368 MMA60323 LART OGG300000117 MMA604705 ABCC6 OGG300000368 MMA60231 METK OGG30000161 MMA61205 ART OGG3000003760 MMA60837 MTAD1 OGG300001383 MMA516025 ART OGG3000001728 MMA60837 MTAD1 OGG300000428 MMA516025 BS10 OGG3000001728 MMA20184 MTAD1 OGG300000467 MMA516025 BS10 OGG3000001633 MMA50183 MTAD1 OGG300000467 MMA516025 BS14 OGG3000001633 MMA501815 MTAT1 OGG300000467 MMA516025 BS14 OGG3000001633 MMA501374 NTPL3 OGG300000467 MMA501805 BS14 OGG3000001638 MMA501875 NTMA OGG300000467 MMA501805 BS15 OGG3000005721 MMA607876 NTMA20805 MMA501805 C17TN5 OGG30000778 MMA607876 NMA501805 MMA501805 C17TN5 OGG30000781 MMA607875 OFFN OGG300008184 <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>						
ABCG6 OGG200000388 MIM602324 MAK OGG200001361 MIM61402 ADGRV1 OGG300008439 MIM604323 MITAD1 OGG300001351 MIM616000 ALN1 OGG300007840 MIM604323 MITAD1 OGG300001453 MIM616000 ALM51 OGG300001522 MIM610444 MITAD4 OGG3000004539 MIM616000 BIS12 OGG3000014279 MIM610144 MTAD4 OGG300000457 MIM630108 BIS12 OGG30000014279 MIM610143 MIV77A OGG300000417 MIM630109 BIS3 OGG30000014279 MIM600144 MIV77A OGG300001012 MIM630199 BIS3 OGG3000001429 MIM600145 NIM27A OGG30000122 MIM60148 BIS4 OGG3000005512 MIM601498 NINL1 OGG300001012 MIM616089 BIS7 OGG300000728 MIM601498 NINL OGG300000497 MIM6160498 CINTA OGG300000724 MIM601498 ORT OGG300000120 MIM6161498 DIS7 OGG300000724 <t< td=""><td>ABCA4</td><td>OGG:300000024</td><td>MIM:601691</td><td>LRAT</td><td>OGG:3000009227</td><td>MIM:604863</td></t<>	ABCA4	OGG:300000024	MIM:601691	LRAT	OGG:3000009227	MIM:604863
ADCRIVIL OGG300005109 MIM.00351 MERTIK OGG30000435 MIM.051600 AIPL1 OGG3000023746 MIM.060839 MTND1 OGG300004355 MIM.51600 BIS51 OGG300000582 MIM.209901 MTNDE OGG300004439 MIM.51600 BIS51 OGG300007728 MIM.201684 MTNDE OGG300004677 MIM.51600 BIS52 OGG30000585 MIM.00188 MTT11 OGG300004677 MIM.51600 BIS54 OGG30000585 MIM.00187 NIVA OGG300004677 MIM.501006 BIS5 OGG300000585 MIM.00174 NIZL3 OGG300004677 MIM.501006 BIS5 OGG300000583 MIM.00174 NIZL3 OGG300004677 MIM.501006 BIS5 OGG3000001288 MIM.201898 NIX OGG30000497 MIM.501309 BIS5 OGG30000749 MIM.601788 NIX OGG30000497 MIM.601789 BIS6 OGG30000749 MIM.601789 PNY OGG30000495 MIM.601740 CICMN1F OGG30000778 M	ABCC6	OGG:3000000368	MIM:603234	MAK	OGG:3000004117	MIM:154235
APEL1 OGG-300007810 MIM-608912 MT-ND1 OGG-300000532 MIM-51003 ALMS1 OGG-300007810 MIM-606814 MT-ND4 OGG-300000532 MIM-51003 BES1 OGG-300000582 MIM-610631 MT-ND4 OGG-3000004-67 MIM-51003 BES12 OGG-300000583 MIM-610148 MT-ND5 OGG-3000004-67 MIM-51003 BES3 OGG-3000004103 MIM-601631 MYO7A OGG-3000004-67 MIM-53050 BES3 OGG-300000403 MIM-601631 MYO7A OGG-300004-60 MIM-601631 BES4 OGG-300000749 MIM-601630 NRE OGG-300004-610 MIM-601632 BES5 OGG-3000072840 MIM-601630 NRE OGG-300004-610 MIM-601632 BES7 OGG-300007284 MIM-601768 OGG-300000749 MIM-601632 MIM-601632 CITONES OGG-300000749 MIM-601768 OGG-3000000585 MIM-601642 CITONES OGG-300000178 MIM-601768 OGG-3000000585 MIM-601642 CITONES OGG-300000178	ADGRV1	OGG:3000084059	MIM:602851	MERTK	OGG:3000010461	MIM:604705
ALMS1 OGG300007840 MMA60844 MT-ND4 OGG300004538 MMA51603 BBS1 OGG300007973 MIM01018 MT+ND4 OGG300004539 MIM051604 BBS12 OGG3000079738 MIM01018 MT+ND6 OGG30000457 MIM051018 BBS2 OGG300000585 MIM060118 MTV07 OGG30000447 MIM269708 BBS2 OGG300000585 MIM060374 NMP11 OGG300001002 MIM060488 BBS3 OGG300000585 MIM060750 NP1 OGG300001002 MIM060488 BBS5 OGG300007788 MIM060750 NP1 OGG300005956 MIM300757 BBS5 OGG30000772 MIM060752 OPN1 OGG300005956 MIM30072 BBS7 OGG30000778 MIM060752 OPN1 OGG300005956 MIM30072 C12TNF5 OGG300000778 MIM060751 PN1 OGG30000558 MIM460752 C12TNF5 OGG300000778 MIM60751 PN1 OGG30000538 MIM60718 C12TNF5 OGG300000775 MIM60751	AIPL1	OGG:3000023746	MIM:604392	MT-ND1	OGG:3000004535	MIM:516000
BR51 OGG:3000079/738 MMX:00PM1 MT-ND41 OGG:300000443 MMX:1604 BBS10 OGG:300004537 MMX:61048 MT-ND6 OGG:300004547 MMX:21608 BBS2 OGG:300000585 MMX:61063 MT07A OGG:300000447 MMX:27603 BBS2 OGG:300000585 MMX:60630 NR1 OGG:3000010002 MMX:604485 BBS4 OGG:30000055512 MMX:60650 NR1 OGG:300004942 MMX:604485 BBS7 OGG:30000055171 MMX:60768 DAT OGG:300004942 MMX:60768 BBS7 OGG:3000005517 MMX:60752 OFN1 LW OGG:300004942 MMX:60768 BBS7 OGG:3000000778 MMX:60161 PXX6 OGG:300000595 MMX:60762 CCH15 OGG:3000000778 MMX6:0162 PCAFE OGG:300000595 MMX:61642 CCH23 OGG:3000000138 MMX:61042 PCAFE OGG:300000596 MMX:61042 CCH24 OGG:300000139 MMX:61042 PCAFE OGG:300005146 MMX:610432 CFH3 OGG:30	ALMS1	OGG:3000007840	MIM:606844	MT-ND4	OGG:3000004538	MIM:516003
BR510 CGG 3000079738 MMA610148 MT-ND6 CGG 3000014507 MIM51009 BB512 CGG 300000583 MMA610681 MT-TL CGG 3000004607 MIM520050 BB54 CGG 300000585 MMA606151 MTV7A CGG 3000014002 MIM620870 BB54 CGG 300000585 MMA60050 NRL CGG 3000014001 MIM640870 BB54 CGG 3000005251 MMA60350 NRL CGG 300004901 MIM640870 BB55 CGG 300007739 MIM60750 NYX CGG 300004906 MIM603027 BB54 CGG 300000773 MIM607516 PAX6 CGG 300008080 MIM607520 CIQTNF5 CGG 300000772 MIM607516 PAX6 CGG 300008080 MIM607108 CFP39 CGG 3000001399 MIM60142 PCARE CGG 300008180 MIM61142 CFR4 CGG 300000139 MIM60142 PCE6 CGG 300008184 MIM610422 CFR4 CGG 300000139 MIM60142 PDE6G CG 30000244 MIM610422 CFR4 CGG 300000121	BBS1	OGG:3000000582	MIM:209901	MT-ND4L	OGG:3000004539	MIM:516004
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BRS2 OGG30000583 MIM.608151 NVO7A OGG3000064402 MIM.207033 BBS3/ARL6 OGG300000585 MIM.608747 NR2B OGG3000016402 MIM.602485 BBS5 OGG30000055212 MIM.607974 NR2B OGG3000004901 MIM.602485 BBS5 OGG300007241 MIM.607976 NYX OGG300004976 MIM.602485 BS5 OGG300007789 MIM.607972 OPN1 OGG300004976 MIM.602552 C1QTNFS OGG30000778 MIM.60772 OPN1 OGG300005080 MIM.605157 C1QTNFS OGG300000778 MIM.607142 PCAR OGG300005080 MIM.605157 C1QTNFS OGG300000172 MIM.607142 PCAR OGG300005080 MIM.601142 C1P320 OGG300000172 MIM.607349 PDF64 OGG300005158 MIM.607074 CFH4 OGG300000170 MIM.607349 PDF66 OGG300005158 MIM.607074 CFH3 OGG30000121 MIM.607349 PDF66 OGG300005148 MIM.610726 CLN3 OGG3000001261	BBS12	OGG:3000166379	MIM:610683	MT-TL1	OGG:3000004567	MIM:590050
BRS3ARL6 OGG300005400 MIM60845 NMART1 OGG30001002 MIM608400 BB54 OGG3000102880 MIM600350 NRL OGG30001000 MIM102080 BB57 OGG300012980 MIM603950 NRL OGG300009402 MIM603786 BB57 OGG3000027211 MIM607960 OP1 OGG300009960 MIM603783 BB51 OGG30000778 MIM607786 OP1 OGG300009960 MIM60752 C10TNP5 OGG300000778 MIM300110 PANC2 OGG300009986 MIM607108 C1P23 OGG300000197 MIM300110 PANC2 OGG300000146 MIM607128 C1P30 OGG300000173 MIM510142 PCARE OGG300000145 MIM6114007 C1P41 OGG300000171 MIM50037 PDE66 OGG300000146 MIM610022 C1P1 OGG300001261 MIM600730 PDE66 OGG300000146 MIM610202 C1N3 OGG300001261 MIM600730 PDE18 OGG300000146 MIM610406 C1N3 OGG300001261 MIM607080 <td>BBS2</td> <td>OGG:3000000583</td> <td>MIM:606151</td> <td>MYO7A</td> <td>OGG:3000004647</td> <td>MIM:276903</td>	BBS2	OGG:3000000583	MIM:606151	MYO7A	OGG:3000004647	MIM:276903
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BISS OGG.3000129800 MIM.602500 NRL OGG.30000501 MIM.1020278 BS9 OGG.300002521 MIM.607968 OAT OGG.3000004976 MIM.60339 BS1 OGG.3000027241 MIM.607854 OPA1 OGG.3000004976 MIM.60382 C1QTNF5 OGG.3000007349 MIM.607854 OPA1 OGG.30000025 MIM.60362 CACNA1F OGG.3000000778 MIM.608375 OPN1LW OGG.30000025 MIM.60157 CDP23 OGG.3000001149 MIM.60142 PCARE OGG.300000158 MIM.613425 CERL OGG.3000001121 MIM.60381 PDE6A OGG.30000158 MIM.180071 CHM OGG.30000121 MIM.600742 PDE6G OGG.30000164 MIM.180073 CLN1 OGG.30000121 MIM.600742 PDE6G OGG.300002544 MIM.600742 CLN3 OGG.300001261 MIM.600742 PRCD OGG.300002544 MIM.600743 CLN3 OGG.300001285 MIM.600745 PRF3 OGG.300002544 MIM.607450 CLN4A OGG.3	BBS4	OGG:3000000585	MIM:600374	NR2E3	OGG:3000010002	MIM:604485
BIS7 OGG3000052121 MIM607960 NYX OGG30000242 MIM30078 BIS9 OGG3000027211 MIM60786 OAT OGG30000492 MIM603280 CI CITNF5 OGG30000778 MIM607854 OPN1 OGG300000575 MIM300822 CACNAIF OGG30000611902 MIM60516 PAX6 OGG3000080184 MIM60142 PCARE OGG300005158 MIM613425 CIP230 OGG3000080184 MIM60142 PCARE OGG300005158 MIM613425 CIP44 OGG3000001121 MIM60390 PDE68 OGG3000005164 MIM6108027 CHM OGG3000001121 MIM607042 PDE66 OGG3000005164 MIM607080 CLRA1 OGG3000001261 MIM60785 POC1B OGG3000005184 MIM607301 CLRA1 OGG300000128 MIM60786 PRCD1 OGG300001284 MIM607302 CNGB3 OGG300001285 MIM60786 PRCM1 OGG300001284 MIM607303 CNLRA1 OGG300001286 MIM60786 PRCM1 OGG300001284 MIM607304 <td>BBS5</td> <td>OGG:3000129880</td> <td>MIM:603650</td> <td>NRL</td> <td>OGG:3000004901</td> <td>MIM:162080</td>	BBS5	OGG:3000129880	MIM:603650	NRL	OGG:3000004901	MIM:162080
BBS9 OGG3000027241 MIM607968 OAT OGG3000044/2 MIM6136259 BEST1 OGG300007439 MIM607852 OPN1 OGG30000255 MIM607852 CACNA1F OGG30000778 MIM607160 PANC OGG300000255 MIM607100 CP230 OGG300000778 MIM607160 PANC OGG300000810 MIM607100 CP1230 OGG3000001399 MIM607102 PCARE OGG300000158 MIM180710 CFRL OGG300001397 MIM607030 PDE6A OGG300000158 MIM180071 CFH OGG300001201 MIM607042 PDE6B OGG300000544 MIM180073 CLN31 OGG300001201 MIM607042 PDE6C OGG300000544 MIM60703 CLN33 OGG30000128 MIM607042 PDE6B OGG30000764 MIM60703 CLN633 OGG30000128 MIM607042 PRC1B OGG30000764 MIM60703 CLN643 OGG30000128 MIM607042 PRC1B OGG30000764 MIM60703 CLN644 OGG300001285 MIM607050 <td>BBS7</td> <td>OGG:3000055212</td> <td>MIM:607590</td> <td>NYX</td> <td>OGG:3000060506</td> <td>MIM:300278</td>	BBS7	OGG:3000055212	MIM:607590	NYX	OGG:3000060506	MIM:300278
BEST1 OGG300007439 MIM:607254 OPA1 OGG300000976 MIM:605290 C1QTNF5 OGG300007490 MIM:608752 OPN1LW OGG300008055 MIM:601822 CACNA1F OGG3000064072 MIM:605516 PAX6 OGG300008025 MIM:6017108 CEP290 OGG300008144 MIM:605516 PAX6 OGG300005145 MIM:6017108 CERAL OGG300000375 MIM:605371 PDE64 OGG3000005145 MIM:180072 CHM OGG3000001201 MIM:60597 PDF64 OGG3000005146 MIM:60827 CLN3 OGG3000001261 MIM:60597 PDF64 OGG3000005148 MIM:10073 CLN4 OGG3000001261 MIM:605724 PDE65 OGG3000005148 MIM:101698 CNS3 OGG300001278 MIM:600574 PDE64 OGG3000005148 MIM:101698 CNS3 OGG300001281 MIM:605797 PD1Y1 OGG300000128 MIM:101698 CNS3 OGG300001281 MIM:605769 PR073 OGG300000128 MIM:601576 CNS43 OGG300	BBS9	OGG:3000027241	MIM:607968	OAT	OGG:3000004942	MIM:613349
CIQTNFS OGG3000114902 MIM:608752 OPN1LW OGG300000595 MIM:801822 CACMAIF OGG300000778 MIM:800110 PAKC OGG300008025 MIM:80157 CDP123 OGG3000080184 MIM:601142 PCARE OGG300005808 MIM:801712 CEP30 OGG3000001399 MIM:608381 PDE6A OGG3000005158 MIM:80071 CFH OGG3000001211 MIM:60397 PDE6B OGG3000005146 MIM:80072 CLN3 OGG300001201 MIM:60397 PDF4G OGG3000005146 MIM:800726 CLN3 OGG300001216 MIM:600724 PDE6G OGG3000005264 MIM:602026 CNS43 OGG300001258 MIM:600724 PRCD OGG300002820 MIM:601598 CNS43 OGG300001258 MIM:60724 PRCD OGG300002814 MIM:601598 CNS43 OGG300001286 MIM:120140 PRF531 OGG300002544 MIM:607301 COLA4 OGG300001286 MIM:120140 PRF531 OGG300001294 MIM:607301 COLA43 OGG30	BEST1	OGG:3000007439	MIM:607854	OPA1	OGG:3000004976	MIM:605290
CACNA1F OGG300000778 MIM300110 PANK2 OGG30000802S MIM406157 CDH23 OGG300006140/2 MIM405516 PAX6 OGG3000005168 MIM407108 CPP290 OGG3000001399 MIM50142 PCARE OGG3000005145 MIM1810071 CFR4 OGG3000001399 MIM514370 PDE6A OGG3000005146 MIM180071 CFH OGG300000121 MIM50742 PDE6G OGG3000005146 MIM180022 CLN3 OGG3000007401 MIM600740 PDE6G OGG300005484 MIM502026 CNG81 OGG300001261 MIM600724 PRCD OGG300005426 MIM602026 CNG83 OGG300001261 MIM60726 PRCD OGG30000842 MIM60730 CNLA3 OGG300001261 MIM607265 PRCD OGG3000026121 MIM60730 COL2A1 OGG300001286 MIM120140 PRFF31 OGG3000026121 MIM60730 COL4A3 OGG300001287 MIM203630 RDH12 OGG300002599 MIM606830 CPAV2 OGG300002844 <t< td=""><td>C1QTNF5</td><td>OGG:3000114902</td><td>MIM:608752</td><td>OPN1LW</td><td>OGG:3000005956</td><td>MIM:300822</td></t<>	C1QTNF5	OGG:3000114902	MIM:608752	OPN1LW	OGG:3000005956	MIM:300822
CDH23 OGG3000064072 MIM60516 PAX6 OGG300005180 MIM607108 CEP3Q0 OGG300008114 MIM610142 PCARE OGG300005158 MIM16107108 CERIL OGG30000375 MIM134370 PDE6A OGG300005158 MIM1180071 CFH OGG300001121 MIM300390 PDE6C OGG300005146 MIM180072 CLN3 OGG300001201 MIM6007042 PDE6G OGG300005148 MIM180072 CLN4 OGG300001201 MIM6007042 PE06G OGG300005284 MIM600226 CLR41 OGG300001261 MIM600537 PHY1 OGG300005828 MIM607305 CLR43 OGG300001260 MIM607805 PR0H OGG300008842 MIM607301 CNB1 OGG300001280 MIM120170 PRF3 OGG300001894 MIM607401 COL4A1 OGG300001286 MIM120170 PRF8 OGG300001594 MIM607410 COL4A5 OGG300001287 MIM50361 RDH12 OGG300001594 MIM60830 CPAV2 OGG3000001286 MIM12	CACNA1F	OGG:3000000778	MIM:300110	PANK2	OGG:3000080025	MIM:606157
CEP290 OGG:300008184 MIM:610142 PCARE OGG:3000038939 MIM:613432 CRRL OGG:3000001399 MIM:60831 PDE6A OGG:3000005145 MIM:180071 CFH OGG:3000001375 MIM:134370 PDE6B OGG:3000005148 MIM:180072 CLN3 OGG:30000701 MIM:60742 PDE6G OGG:300002524 MIM:60827 CLN3 OGG:300007121 MIM:600537 POC1B OGG:30000282809 MIM:61784 CN6A3 OGG:300007218 MIM:600537 POC1B OGG:300008842 MIM:61788 CN6B3 OGG:3000055714 MIM:600724 PRCD OGG:300008842 MIM:61789 CN8B3 OGG:300005128 MIM:60780 PRF3 OGG:30000129 MIM:60780 CDL2A1 OGG:300001286 MIM:120170 PRF53 OGG:300001291 MIM:60780 COL4A3 OGG:300001286 MIM:120170 PRF8 OGG:300002999 MIM:60780 COL4A4 OGG:300001286 MIM:120170 PRF8 OGG:300002999 MIM:60170 CRX <td< td=""><td>CDH23</td><td>OGG:3000064072</td><td>MIM:605516</td><td>PAX6</td><td>OGG:3000005080</td><td>MIM:607108</td></td<>	CDH23	OGG:3000064072	MIM:605516	PAX6	OGG:3000005080	MIM:607108
CERKL OGG300001399 MIM.608381 PDE6A OGG3000001515 MIM:18071 CH OGG300000375 MIM:13470 PDE6B OGG3000005158 MIM:180072 CHM OGG3000001121 MIM:607042 PDE6G OGG3000005146 MIM:607032 CLN1 OGG300001201 MIM:607042 PDE6G OGG3000005264 MIM:60703 CLRN1 OGG300001258 MIM:600734 PQC1B OGG300005264 MIM:60704 CNGB1 OGG300001258 MIM:60704 PRCD OGG3000082809 MIM:610598 CNGB3 OGG300001258 MIM:607204 PRCD OGG300009129 MIM:60730 CNLB3 OGG300001280 MIM:60705 PRPF3 OGG300000129 MIM:60730 C0L4A1 OGG300001285 MIM:120170 PRPF8 OGG30000199 MIM:60730 C0L4A4 OGG300001285 MIM:120170 PRPF13 OGG30000196 MIM:60730 C0L4A5 OGG300001286 MIM:120170 PRPF14 OGG30000196 MIM:60741 CR4 OGG30000127	CEP290	OGG:3000080184	MIM:610142	PCARE	OGG:3000388939	MIM:613425
CFH OGG300003075 MIM:134370 PDE6B OGG300000518B MIM:180072 CHM OGG300001121 MIM:000720 PDE6C OGG300000514B MIM:600226 CLN3 OGG300001201 MIM:600370 PDE6G OGG300000514B MIM:600226 CLN4 OGG300001251 MIM:60037 PDE6G OGG300002860 MIM:610226 CNGA3 OGG300001258 MIM:600724 PRCD OGG300008427 MIM:603705 CNGB3 OGG300001276 MIM:600724 PRCD OGG300008427 MIM:603705 CNGB3 OGG300001276 MIM:607080 PRPF13 OGG3000001286 MIM:607080 COLA41 OGG300001286 MIM:120140 PRPF31 OGG300001594 MIM:603701 COL4A3 OGG300001287 MIM:120170 PRPF8 OGG300001594 MIM:608103 COL4A4 OGG300001287 MIM:606210 RDF5 OGG300001610 MIM:180892 CP4V2 OGG300001286 MIM:60812 RH0 OGG300000610 MIM:180892 CP4V2 OGG300000274<	CERKL	OGG:3000001399	MIM:608381	PDE6A	OGG:3000005145	MIM:180071
CHM OGG.300001121 MIM.300390 PDE6C OGG.300001616 MIM.500827 CLN3 OGG.300001201 MIM.600742 PDE6G OGG.300000544 MIM.180073 CLR1 OGG.300001201 MIM.600537 PCH OGG.300002564 MIM.610744 CNGB3 OGG.300001258 MIM.600724 PRCD OGG.30000842 MIM.60730 CNGB3 OGG.3000025741 MIM.6007805 PRPF3 OGG.300001284 MIM.607301 CNL2A1 OGG.300001285 MIM.120140 PRFF31 OGG.300001294 MIM.607301 COL4A3 OGG.300001285 MIM.120170 PRPF8 OGG.300001594 MIM.607301 COL4A4 OGG.300001286 MIM.120170 PRPF3 OGG.300001594 MIM.60830 CR81 OGG.300001287 MIM.303630 RDH12 OGG.300001594 MIM.60830 CV14A5 OGG.300001287 MIM.303630 RDH12 OGG.300001596 MIM.60830 CVP4V2 OGG.3000023418 MIM.60212 RDH5 OGG.300002590 MIM.50830 CVP4V2	CFH	OGG:3000003075	MIM:134370	PDE6B	OGG:3000005158	MIM:180072
CLN3 OGG.300001201 MIM:607042 PDEGG OGG.300001148 MIM:18073 CLRN1 OGG.300007401 MIM:600337 PHYH OGG.3000025264 MIM:50026 CNG31 OGG.300001258 MIM:600734 PCD OGG.300002820 MIM:61784 CNGB1 OGG.300001258 MIM:607205 PRPT OGG.300002812 MIM:607301 CNGB3 OGG.300001280 MIM:120140 PRPF31 OGG.3000026121 MIM:607301 COL4A1 OGG.300001286 MIM:120171 PRPF3 OGG.300001281 MIM:607301 COL4A3 OGG.300001286 MIM:120171 PRPF3 OGG.300001594 MIM:607301 COL4A5 OGG.300001287 MIM:120171 PRPF3 OGG.300001595 MIM:608300 CR1 OGG.300001287 MIM:120171 PRP12 (RDS) OGG.300005959 MIM:608300 CR4 OGG.300001287 MIM:60225 RH0 OGG.300000599 MIM:608300 CR4 OGG.300001286 MIM:60226 RH0 OGG.300000610 MIM:180380 CYP4V2	CHM	OGG:3000001121	MIM:300390	PDE6C	OGG:3000005146	MIM:600827
CLRN1 OGG300007401 MIM:606397 PHYH OGG3000025264 MIM:602026 CNGA3 OGG300001261 MIM:60053 POC1B OGG3000282809 MIM:61744 CNGB1 OGG3000054714 MIM:600724 PRCD OGG300008842 MIM:60363 CNGB3 OGG3000054714 MIM:607805 PRPA OGG3000026121 MIM:60361 CNLA1 OGG300001280 MIM:120100 PRPF31 OGG300001291 MIM:603700 COL4A3 OGG300001285 MIM:120070 PRPF4 OGG300001594 MIM:603700 COL4A4 OGG300001287 MIM:20131 PRPH2 (RDS) OGG300005950 MIM:60380 COL4A5 OGG300001287 MIM:606212 RDH12 OGG300005959 MIM:601617 CRX OGG3000023418 MIM:608172 RLB7 OGG300006101 MIM:18080 CYP4V2 OGG30000244 MIM:608172 RLB7 OGG300006101 MIM:18080 CYP4V2 OGG300002297 MIM:601548 RP1 OGG300006101 MIM:18030757 EL0VL4 OGG300	CLN3	OGG:3000001201	MIM:607042	PDE6G	OGG:3000005148	MIM:180073
CNGA3 OGG300001261 MIM:600053 POC1B OGG3000282809 MIM:61784 CNGB1 OGG300001288 MIM:600724 PRCD OGG3000768206 MIM:610588 CNGB3 OGG3000025604 MIM:607805 PRPF3 OGG300009129 MIM:607301 COL2A1 OGG300001280 MIM:120140 PRPF31 OGG300001594 MIM:607301 COL4A3 OGG300001286 MIM:120170 PRPF8 OGG300001594 MIM:607300 COL4A4 OGG300001286 MIM:120171 PRPF12 OGG300001594 MIM:607300 COL4A5 OGG300001286 MIM:120171 PRPF2 OGG300001594 MIM:607300 COL4A5 OGG300001286 MIM:20171 PRPF2 OGG300001595 MIM:601617 CR81 OGG300001466 MIM:60225 RH0 OGG3000005959 MIM:601617 CR4 OGG3000028440 MIM:608172 RL8P1 OGG300006101 MIM:180307 CP4V2 OGG300006755 MIM:601572 RP2 OGG300006101 MIM:180307 EFMP1 OGG30000	CLRN1	OGG:3000007401	MIM:606397	PHYH	OGG:3000005264	MIM:602026
CNGB1 OGG.300001258 MIM.600724 PRCD OGG.3000768206 MIM.610598 CNGB3 OGG.30000267114 MIM.60080 PROM1 OGG.3000008842 MIM.607305 CNLB3 OGG.3000026504 MIM.607805 PRPF31 OGG.300002121 MIM.607300 COL2A1 OGG.300001285 MIM.120140 PRPF31 OGG.300001294 MIM.607300 COL4A3 OGG.300001286 MIM.120170 PRPF8 OGG.300001594 MIM.607300 COL4A4 OGG.300001287 MIM.120170 PRPF12 OGG.3000015959 MIM.607300 COL4A5 OGG.300001287 MIM.60210 RDH5 OGG.3000005959 MIM.601617 CRX OGG.30000220148 MIM.608172 RIB91 OGG.3000005959 MIM.606629 DHDD5 OGG.300002202 MIM.601728 RIB91 OGG.300000128 MIM.180380 CYP4V2 OGG.300002407 MIM.605512 RP2 OGG.300006101 MIM.180396 EFEMP1 OGG.300002790 MIM.613596 RPGR OGG.300005011 MIM.180596	CNGA3	OGG:3000001261	MIM:600053	POC1B	OGG:3000282809	MIM:614784
CNGB3 OGG:3000054714 MIM:605080 PROM1 OGG:3000008842 MIM:607805 CNNM4 OGG:300001280 MIM:120140 PRPF3 OGG:300002611 MIM:607301 COL2A1 OGG:300001280 MIM:120140 PRPF8 OGG:3000026121 MIM:607300 COL4A3 OGG:300001286 MIM:120170 PRPF8 OGG:300005961 MIM:67300 COL4A5 OGG:300001287 MIM:303630 RDH12 OGG:300005959 MIM:608170 CR81 OGG:3000023418 MIM:60225 RHO OGG:30000610 MIM:18080 CYP4V2 OGG:30000285440 MIM:608142 RIMS1 OGG:30000610 MIM:18080 CYP4V2 OGG:30000285440 MIM:608172 RLBP1 OGG:30000617 MIM:18080 CYP4V2 OGG:30000279 MIM:61548 RP1 OGG:30000617 MIM:18080 EFEMP1 OGG:30000279 MIM:61548 RP1 OGG:300006103 MIM:18080 GNAT1 OGG:300002779 MIM:61356 RPGR OGG:300006103 MIM:181031 GNAT2	CNGB1	OGG:3000001258	MIM:600724	PRCD	OGG:3000768206	MIM:610598
CNNM4 OGG.300026504 MIM:607805 PRF3 OGG.300009129 MIM:607301 COL2A1 OGG.300001280 MIM:120140 PRF51 OGG.300001594 MIM:607300 COL4A3 OGG.300001285 MIM:120070 PRPF8 OGG.300001594 MIM:607300 COL4A4 OGG.300001286 MIM:120131 PRPH2 (RDS) OGG.300005951 MIM:608010 COL4A5 OGG.300002418 MIM:604210 RDH5 OGG.300005959 MIM:608010 CR1 OGG.3000024544 MIM:604210 RDH5 OGG.300000610 MIM:180380 CYP4V2 OGG.30000285440 MIM:60814 RIMS1 OGG.300006101 MIM:180380 CYP4V2 OGG.3000029947 MIM:601548 RP1 OGG.300006101 MIM:180397 ELOVL4 OGG.300002020 MIM:61548 RP1 OGG.300006101 MIM:180397 ELOVL4 OGG.300006785 MIM:61548 RP1 OGG.300006101 MIM:180397 ELOVL4 OGG.300006785 MIM:61548 RP1 OGG.300006101 MIM:180397 EYS	CNGB3	OGG:3000054714	MIM:605080	PROM1	OGG:3000008842	MIM:604365
COL2A1 OGG:300001280 MIM:120140 PRPF31 OGG:300002121 MIM:60619 COL4A3 OGG:300001285 MIM:120070 PRPF8 OGG:300005961 MIM:179605 COL4A4 OGG:300001286 MIM:120131 PRPL2 (RDS) OGG:300005961 MIM:179605 COL4A5 OGG:300001287 MIM:303630 RDH12 OGG:300005959 MIM:608130 CRB1 OGG:3000023418 MIM:604210 RDH5 OGG:300000610 MIM:60817 CRX OGG:30000285440 MIM:608122 RLBP1 OGG:300006017 MIM:180809 CP4V2 OGG:3000029947 MIM:608172 RLBP1 OGG:300006101 MIM:180809 EFEMP1 OGG:300002020 MIM:608512 RP2 OGG:300006102 MIM:180809 FAM161A OGG:300006785 MIM:605152 RP2 OGG:300006103 MIM:19307 FYS OGG:300002709 MIM:13930 RPGR OGG:300006103 MIM:60819 GNAT1 OGG:300002780 MIM:602851 SAG OGG:300006295 MIM:601819 GP898	CNNM4	OGG:3000026504	MIM:607805	PRPF3	OGG:3000009129	MIM:607301
COL4A3 OGG.300001285 MIM:12070 PRPF8 OGG.300001594 MIM:60700 COL4A4 OGG.300001286 MIM:120131 PRPH2 (RDS) OGG.300005961 MIM:608830 COL4A5 OGG.300001287 MIM:303630 RDH12 OGG.300005959 MIM:608170 CRB1 OGG.3000023418 MIM:602225 RHO OGG.300002399 MIM:601617 CRX OGG.30000285440 MIM:608172 RLBP1 OGG.300002299 MIM:60820 DHDDS OGG.300002202 MIM:608172 RLBP1 OGG.300006101 MIM:180300 EFEMP1 OGG.300002202 MIM:601548 RP1 OGG.300006102 MIM:13037 ELOVL4 OGG.300006785 MIM:601548 RP1 OGG.300006101 MIM:3937 ELOVL4 OGG.300002279 MIM:612424 RP65 OGG.300006103 MIM:312610 GNAT1 OGG.300002780 MIM:13930 RPGR OGG.300006247 MIM:30389 GPR98 OGG.300000278 MIM:139340 R51 OGG.3000002978 MIM:602456 GV12	COL2A1	OGG:3000001280	MIM:120140	PRPF31	OGG:3000026121	MIM:606419
COL4A4 OGG:300001286 MIM:120131 PRPL2 (RDS) OGG:3000005961 MIM:179605 COL4A5 OGG:300001287 MIM:303630 RDH12 OGG:3000015264 MIM:60830 CRB1 OGG:3000023418 MIM:604210 RDH5 OGG:3000005959 MIM:601617 CRX OGG:300002416 MIM:602225 RHO OGG:3000022999 MIM:606629 CYP4V2 OGG:300002201 MIM:60814 RIMS1 OGG:300006101 MIM:80800 EFEMP1 OGG:300002202 MIM:601548 RP1 OGG:300006101 MIM:80900 EFEMP1 OGG:300006102 MIM:601548 RP1 OGG:300006102 MIM:80900 ELOVL4 OGG:300006785 MIM:601548 RP1 OGG:300006102 MIM:80069 FAM161A OGG:3000084100 MIM:612424 RP665 OGG:300006103 MIM:801646 GNAT1 OGG:300002790 MIM:139300 RPGR OGG:300006274 MIM:80089 GNAT2 OGG:300002780 MIM:602851 SAG OGG:300006274 MIM:602722 GNAT2	COL4A3	OGG:3000001285	MIM:120070	PRPF8	OGG:3000010594	MIM:607300
COL4A5 OGG:300001287 MIM:303630 RDH12 OGG:3000145226 MIM:60830 CRB1 OGG:3000023418 MIM:604210 RDH5 OGG:3000005959 MIM:601617 CRX OGG:30000285440 MIM:608214 RIMO OGG:3000022999 MIM:60629 DHDDS OGG:3000079947 MIM:608144 RIMS1 OGG:300006017 MIM:60629 DHDDS OGG:300002020 MIM:601548 RP1 OGG:300006101 MIM:3037 ELOVL4 OGG:300006785 MIM:605512 RP2 OGG:30000612 MIM:180069 FAM161A OGG:300006785 MIM:612424 RPE65 OGG:30000613 MIM:180696 FAM161A OGG:30000279 MIM:613936 RPGR OGG:30000613 MIM:180469 GNAT1 OGG:300002779 MIM:13930 RPGRIP1 OGG:300006295 MIM:60389 GNAT2 OGG:3000002780 MIM:13931 SEMA4A OGG:300006295 MIM:607292 GVCA1A OGG:3000002978 MIM:60364 SNRNP200 OGG:300006295 MIM:607292 GUCA1A	COL4A4	OGG:3000001286	MIM:120131	PRPH2 (RDS)	OGG:3000005961	MIM:179605
CRB1 OGG:300023418 MIM:604210 RDH5 OGG:300005959 MIM:601617 CRX OGG:300001406 MIM:602225 RHO OGG:3000022999 MIM:606629 CYP4V2 OGG:3000029947 MIM:60814 RIMS1 OGG:30000617 MIM:606629 DHDDS OGG:300002202 MIM:60174 RLBP1 OGG:30000617 MIM:3090 EFEMP1 OGG:300006785 MIM:601548 RP1 OGG:300006102 MIM:3077 ELOVL4 OGG:300006785 MIM:605512 RP2 OGG:300006121 MIM:300757 EYS OGG:300002779 MIM:612424 RPE65 OGG:300006103 MIM:312610 GNAT1 OGG:300002779 MIM:13930 RPGR OGG:300006247 MIM:605846 GNAT2 OGG:300002780 MIM:602851 SAG OGG:3000064218 MIM:607292 GVCA1A OGG:300002978 MIM:60364 SNRNP200 OGG:300002302 MIM:604646 GUC41B OGG:300002979 MIM:60364 SNRNP200 OGG:300002302 MIM:604646 GUC41B <t< td=""><td>COL4A5</td><td>OGG:3000001287</td><td>MIM:303630</td><td>RDH12</td><td>OGG:3000145226</td><td>MIM:608830</td></t<>	COL4A5	OGG:3000001287	MIM:303630	RDH12	OGG:3000145226	MIM:608830
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EFEMP1 OGG:300002202 MIM:601548 RP1 OGG:300006101 MIM:3937 ELOVL4 OGG:300006785 MIM:605512 RP2 OGG:300006102 MIM:300757 EYS OGG:3000346007 MIM:612424 RPE65 OGG:300006103 MIM:312610 GNAT1 OGG:300002779 MIM:613596 RPGR OGG:3000057096 MIM:30839 GNAT2 OGG:300002780 MIM:139340 RS1 OGG:300006247 MIM:30839 GRK1 OGG:300006011 MIM:602851 SAG OGG:3000064218 MIM:607292 GUCA1A OGG:300002978 MIM:600364 SNRNP200 OGG:300002302 MIM:601664 GUC21B OGG:300002979 MIM:600364 SNRNP200 OGG:3000055812 MIM:609868 GUC21B OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:180867 GUC21D OGG:300003614 MIM:610453 TOPORS OGG:300007287 MIM:60280 GUC21D OGG:300003617 MIM:602870 TULP1 OGG:300007287 MIM:60280 GUC41B <td>DHDDS</td> <td>OGG:3000079947</td> <td>MIM:608172</td> <td>RLBP1</td> <td>OGG:3000006017</td> <td>MIM:180090</td>	DHDDS	OGG:3000079947	MIM:608172	RLBP1	OGG:3000006017	MIM:180090
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GNAT2 OGG:300002780 MIM:139340 RS1 OGG:300006247 MIM:30839 GPR98 OGG:3000084059 MIM:602851 SAG OGG:300006295 MIM:181031 GRK1 OGG:300002978 MIM:180381 SEMA4A OGG:3000064218 MIM:607292 GUCA1A OGG:300002978 MIM:600364 SNRNP200 OGG:3000023020 MIM:601664 GUCA1B OGG:300002979 MIM:602275 SPATA7 OGG:300005812 MIM:609868 GUCY2D OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:188266 HGSNAT OGG:300003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPDH1 (RP10) OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:60280	GNAT1	OGG:3000002779	MIM:139330	RPGRIP1	OGG:3000057096	MIM:605446
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GRK1 OGG:300006011 MIM:180381 SEMA4A OGG:3000064218 MIM:607292 GUCA1A OGG:300002978 MIM:600364 SNRNP200 OGG:3000023020 MIM:601664 GUCA1B OGG:300002979 MIM:602275 SPATA7 OGG:3000055812 MIM:609868 GUCY2D OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:188826 HGSNAT OGG:300003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPG1 OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:607694	GPR98	OGG:3000084059	MIM:602851	SAG	OGG:3000006295	MIM:181031
GUCA1A OGG:300002978 MIM:600364 SNRNP200 OGG:3000023020 MIM:601664 GUCA1B OGG:300002979 MIM:602275 SPATA7 OGG:3000055812 MIM:609868 GUCY2D OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:188826 HGSNAT OGG:300003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPG1 OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	GRK1	OGG:3000006011	MIM:180381	SEMA4A	OGG:3000064218	MIM:607292
GUCA1B OGG:300002979 MIM:602275 SPATA7 OGG:3000055812 MIM:609868 GUCY2D OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:188826 HGSNAT OGG:300003610 MIM:610453 TOPORS OGG:300007287 MIM:609507 IMPDH1 (RP10) OGG:300003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPG1 OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	GUCA1A	OGG:3000002978	MIM:600364	SNRNP200	OGG:3000023020	MIM:601664
GUCY2D OGG:300003000 MIM:600179 TIMP3 OGG:300007078 MIM:18826 HGSNAT OGG:3000138050 MIM:610453 TOPORS OGG:3000010210 MIM:609507 IMPDH1 (RP10) OGG:300003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPG1 OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	GUCA1B	OGG:3000002979	MIM:602275	SPATA7	OGG:3000055812	MIM:609868
HGSNAT OGG:3000138050 MIM:610453 TOPORS OGG:3000010210 MIM:609507 IMPDH1 (RP10) OGG:3000003614 MIM:146690 TULP1 OGG:3000007287 MIM:602280 IMPG1 OGG:3000003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	GUCY2D	OGG:3000003000	MIM:600179	TIMP3	OGG:3000007078	MIM:188826
IMPDH1 (RP10) OGG:3000003614 MIM:146690 TULP1 OGG:300007287 MIM:602280 IMPG1 OGG:300003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	HGSNAT	OGG:3000138050	MIM:610453	TOPORS	OGG:3000010210	MIM:609507
IMPG1 OGG:3000003617 MIM:602870 USH1G OGG:3000124590 MIM:607696	IMPDH1 (RP10)	OGG:3000003614	MIM:146690	TULP1	OGG:3000007287	MIM:602280
	IMPG1	OGG:3000003617	MIM:602870	USH1G	OGG:3000124590	MIM:607696

IMPG2	OGG:3000050939	MIM:607056	USH2A	OGG:3000007399	MIM:608400
IQCB1	OGG:3000009657	MIM:609237	VCAN	OGG:3000001462	MIM:118661
KCNV2	OGG:3000169522	MIM:607604	WDR19	OGG:3000057728	MIM:608151
KLHL7	OGG:3000055975	MIM:11119	Other	N/A	N/A
LCA5	OGG:3000167691	MIM:611408	Inconclusive	N/A	N/A

Table 2 (continued)

^a The user may select one, two or more genes in case clinically relevant variants are found in more than one gene. This list may be edited with newer additions in case other genes are found in the Portuguese population with IRDs

The family linkage section allows simple viewing of the details of affected family members that are also part of the registry. At the end of each visit, a free text area is available for comments (follow-up, imaging, prescription, etc.).

Longitudinal data is captured through specific follow-up forms. The platform allows retrospective data introduction. As the program develops, and through alignment with international data collection for IRD clinical registries, the IRD-PT core data set may be modified or extended to include additional key clinical variables.

Data analysis and graphical displays

Since the *retina.pt* was designed to be both a registry and a research tool, data export and analysis features are very important. A search engine that allows data filtering is available for the user to search specific anonymized data, such as the total number of affected patients or the total number of affected families with a certain diseasecausing gene, clinical diagnosis, BCVA level, etc. Furthermore, the platform offers statistical tools for simple analyses and these are also available for the IRD-PT module (Figs. 1, 2). For more sophisticated analyses, users can export their own data on *excel* format and analyze it as they see fit. Data are aggregated in an anonymized fashion, without identification of the individual patients.

Participant characteristics

So far, the *retina.pt* platform has been approved by the Human Research Ethics Committee (HREC)/Institutional Review Board (IRB) of 52 health care providers across Portugal. Each of these hospitals/clinics has established the necessary infrastructure to support rapid rollout of site and patient recruitment, data collection, and data transfer. One-hundred and thirty five users (doctors/investigators) have applied for credentials to access the registry, and 58 of these have already included patient data. To date, there are over 1800 participants (patients) and over 30,000 consultations included in the registry. In mid 2019, the IRD-PT module was pre-launched at *Centro Hospitalar e Universitário de Coimbra* (CHUC), the only Portuguese health care provider (HCP) that is a member of the ERN-EYE, and the largest reference

center for IRDs in Portugal. The idea of testing the registry in one dedicated center before its national debut was aimed to identify possible problems during data completion, test the time spent in data entry, and detect information gaps or system inaccuracies. The registry proved fully functional, fast and easy to use. As of April 1st 2020, finalized data from 537 participants were available for this preliminary analysis. Considering the Portuguese population (~ 10 million inhabitants), this number corresponds to roughly 1/6 of the total estimated cases of IRDs in Portugal. The distribution of the clinical diagnoses and their relative frequency among the included participants is shown in Table 4. As illustrated in Fig. 3, syndromic (14%) and non-syndromic retinitis pigmentosa (36%) account for 50% of the clinical diagnoses. The percentage of genetically solved and unsolved cases of syndromic and non-syndromic RP is shown in Fig. 4. Of all participants included in the IRD-PT registry to date, 57% are women and the mean age at the index visit was 39.27 ± 19.03 years. Average baseline BCVA was 54.36 ± 27.22 and final BCVA was 47.64 ± 28.92 ETDRS letters.

Discussion

Appropriate design, implementation and deployment of patient registries enables rapid decision making and ongoing data mining, ultimately leading to improved patient outcomes [7, 19, 20]. In the specific field of rare diseases, the use of registries increases research accessibility for individuals, while providing clinicians/ investigators with a coherent data ecosystem necessary to boost research. The IRD-PT module of retina. pt will facilitate the efficient capture of accurate, longitudinal, country-wide data for IRDs. The registry will provide valuable information on disease prevalence, genomic landscape, genotype-phenotype correlations and natural history of IRDs, which is currently an unmet need in Portugal. Furthermore, the registry will facilitate patient selection for newly approved treatments or enrollment in clinical trials. The use of a webbased data storage system allows the registry to extend recruitment across multiple centers in the country. The modular design and scalable nature of the framework

Field	Type of entry	Answer	Available options
1. Patient ID	Free text	Mandatory	
2. Date of birth	Date format	Mandatory	
3. Sex	Select from list	Mandatory	Male; female
4. Date of diagnosis	Date format	Mandatory	
5. Clinical diagnosis	Select from list (allows selection of more than one option)	Mandatory	See Table 1
6. Consanguinity	Select from list	Mandatory	Yes; no; suspected
7. Family history	Select from list	Mandatory	Yes; no; suspected
7.1. Family linkage section (only shows if the user answered Yes to the previous question)	I Allows introduction of one or multiple affected family memb father; son; daughter; uncle; aunt; cousin; grandfather; gran page in case he/she has consented to be part of the registr	oers, including ndmother; oth ry	their family relation to the patient (brother; sister; mother; er) and Hospital ID which has a hyperlink to that patient's
8. Signs and symptoms	Select from list (allows selection of more than one option)	Mandatory	Nyctalopia (HP:0000662); decreased VA (HP:0000529); pho- tophobia (HP:0000613); color vision defects (HP:0000551); central scotoma (HP:000603); constricted visual field (HP:0001133); photopsia (HP:0002316); migraine mus (HP:0,000,639); headache (HP:0002315); migraine (HP:0002076); visual hallucinations (HP:0002367); other
9. Age of onset of symptoms	Select from list	Mandatory	at birth; < 5; 6–10; 11–20; 21–30; 31–50; > 51
10. Syndromic features	Select from list	Mandatory	Yes/no
10.1. Syndromic features list (only shows if the user answered yes to the previous question)	Select from list (allows selection of more than one option)	Optional	Hearing loss/deafness (HP:0008527); obesity (HP:0001513); hypogonadism (HP:0000135); diabetes mellitus (HP:0000819); diabetes insipidus (HP:0000873); polydactyly (HP:0010442); other skeletal abnormalities (HP:0000924); cognitive impairment (HP:0100543); developmental delay (HP:0001263); seizures (HP:0001250); ataxia (HP:0001251); dysarthria (HP:0001260); renal insufficiency (HP:000083); other
11. Genetic testing	Select from list	Mandatory	Yes/no
11.1. Type of test (only shows if the user answered yes to genetic testing)	Select from list (allows selection of more than one option)	Optional	Sanger sequencing; NGS panel; WES; MLPA; don't know; other
11.2. Gene (only shows if the user answered yes to genetic testing)	Select from list (allows selection of more than one option)	Optional	See Table 2
11.3. Variants ^a (only shows if the user answered yes to genetic testing)	Free text	Optional	
11.4. Classification of variants (ACMG) (only shows if the user answered yes to genetic testing)	Select from list (for each introduced variant)	Optional	Pathogenic; likely pathogenic; VUS
BCVA ^b	Select from list	Mandatory	From 20/1000 to 20/10
IObp	Free text	Optional	Only accepts numbers from 01 to 99

Field	Type of entry	Answer	Available options
Additional diagnoses ^b	Select from list (allows selection of more than one option)	Optional	Amblyopia (HP:0000646); cataract (HP:0000518); CNV (HP:0011506); CME (HP:0011505); glaucoma (HP:0000501); ERM (HP:0100014); macular hole (HP:0011508); lamellar hole (HP:0001103); macular pseudohole (HP:0001103); vitreomacular traction (HP:0031151); retinal detachment (HP:0000561); keratoconus (HP:0000563); strabismus (HP:0000486); other
Previous treatments ^b	Select from list (allows selection of more than one option)	Optional	Vitreoretinal surgery; strabismus surgery; glaucoma surgery; YAG laser capsulotomy; corneal transplant; cataract surgery; intravitreal injection; subretinal injection; laser photocoagu- lation; refractive surgery; other
DOB date of birth, NGS next generation sequencing, WES whole e: uncertain significance, BCVA best corrected visual acuity, IOP intra ^a Apart from listing the variants as free text, an icon is available fc	xome sequencing, <i>MLP</i> A multiplex ligation-dependent probe amplific locular pressure, <i>CNV</i> choroidal neovascularization, <i>CME</i> cystoid macu or the upload of the raw sequencing file	cation, <i>ACMG</i> Ar ular edema, <i>ERN</i>	nerican College of Medical Genetics and Genomics, VUS variant of lepiretinal membrane
^b These fields appear separately for the right and left eye			

Table 3 (continued)



used to deploy the IRD-PT registry make it easily adaptable over time, ensuring its long-term sustainability. Furthermore, the use of domain-specific ontologies adds value to data, through an integrated knowledge base that is searchable and comparable by user and by machines [17, 21]. In fact, by resorting to common data elements, core outcome sets, and standardized data structures, the IRD-PT module can support the exchange of data across datasets, facilitating the connection to other registries at an international level. The interoperability of this registry by means of data harmonization is a key feature pointing to its utility and scalability. Another important issue of a web-based registry is usability, i.e. the capacity of a software system to provide conditions for its users to perform the tasks satisfactorily, effectively, and efficiently. Ophthalmologists have limited time with patients during office visits, and electronic health record (EHR) use requires a substantial portion of that time, therefore affecting productivity [22, 23]. The *retina.pt* registry combines a user-friendly platform and reduced load of data entry with the possibility to generate a *pdf* document that can be saved, printed or copied to the hospital EHR system, thus eliminating the need for duplicate records. Additionally, there is also the possibility of EHR third party applications with structured information to deliver their data directly to specific subfields of the registry, thus enabling a quick fill in process. The detailed information provided on Table 3 regarding data capture for the IRD-PT may be used to modify EHR systems to allow for direct data transfer. Finally, the versatility of the platform, makes it possible to serve as electronic case report form (eCRF) for upcoming observational, natural-history or post-market authorization studies.

The IRD-PT is not exempt of limitations. An important principle in registry design is to reduce the load of data entry. This does not come without a price. By limiting the data that is considered mandatory to a minimum, there may be incomplete information/missing data for some included subjects concerning unanswered non-mandatory fields. Another limitation is that grading systems/ levels for the symptoms or degree of impairment are not available. The fact that symptoms are simply marked as present/not present prevents a precise characterization of these symptoms during the disease course. Finally, since each user is responsible for its own data entry, we cannot be sure about the accuracy of its contents. This may be particularly problematic when a case is considered molecularly solved or unsolved. Misinterpretation of the genetic findings is not uncommon, which may lead to selection bias regarding the number of molecularly solved/unsolved cases.



Conclusions

We have described here the principles behind the design, development and deployment of a web-based software tool that forms the basis of a nation-wide registry for IRDs. The pre-launch of the IRD-PT module in the largest Portuguese referral center for IRDs (CHUC), allowed to test the functionalities of the registry and enroll the first 537 IRD patients, roughly 1/6 of the total estimated cases of IRDs in Portugal. Now that the module is fully working, recruitment will be extended to other Portuguese hospitals. Judging from the enthusiasm and adherence observed with the launch of the *retina.pt* platform, we believe that the IRD-PT registry will be rapidly adopted by the Portuguese ophthalmologists managing IRD patients. Our hope is to generate important knowledge and collect high-quality data on the epidemiology, genomic landscape, genotype-phenotype correlations and natural history of IRDs in Portugal. This will both boost and excel clinical research in the field of IRDs in our country, while facilitating patient access to clinical trials or new therapies.

Methods

Registry design

The IRD-PT is a clinical/genetic research registry. Its main goal is to create a national, web-based registry of IRDs in Portugal that allows to study their prevalence, genomic profile, genotype-phenotype correlations and natural history. Also, the registry may assist in the recruitment of participants for new treatments/clinical trials, and provide support for the establishment of disease-specific standards and care. The IRD-PT registry is included in the retina.pt platform (https://www. retina.com.pt), which was developed by the Portuguese Retina Study Group (GER, www.ger-portugal.com). The retina.pt registry deployed in 2017 to fulfil a vital component on patient-centered care for retinal diseases. It collects data on individuals diagnosed with retinal diseases, from several sites across Portugal, with over 1800 participants and over 30,000 consultations to date. The IRD-PT is a module interacting with the *retina.pt* core system. The core system provides a range of basic functions used for patient data management, while the

Table 4 Distribution of the clinical IRD diagnoses and theirrelative frequency among the 537 subjects includedin the IRD-PT registry

Clinical diagnosis	n	Relative frequency (%)
Non-syndromic RP	192	35.75
Syndromic RP	74	13.78
Cone/cone-rod dystrophy	62	11.55
Stargardt disease	27	5.03
PXE	21	3.91
Pattern dystrophy	20	3.72
ADOA (Kjer)	14	2.61
Leber congenital amaurosis	12	2.23
Best vitelliform macular dystrophy	12	2.23
Foveal hypoplasia	11	2.05
X-linked retinoschisis	10	1.86
PPRCA	7	1.30
Achromatopsia	6	1.12
Ocular/oculocutaneous albinism	6	1.12
CACD	6	1.12
Choroideremia	6	1.12
CSNB	5	0.93
Coloboma	5	0.93
ARB	4	0.74
Bietti crystalline dystrophy	4	0.74
Fundus albipunctatus	4	0.74
MIDD	4	0.74
Gyrate atrophy of choroid and retina	3	0.56
Goldmann-Favre syndrome/ESCS	3	0.56
Stickler/Wagner syndrome	3	0.56
Cuticular drusen/C3 glomerulopathy	3	0.56
LORD	3	0.56
LHON	3	0.56
ADVIRC	2	0.37
Retinitis punctata albescens	2	0.37
Alport syndrome	2	0.37
NCMD	1	0.19

RP retinitis pigmentosa, *PXE* pseudoxanthoma elasticum, *ADOA* autosomal dominant optic atrophy, *PPRCA* pigmented paravenous retinochoroidal atrophy, *CACD* central areolar choroidal dystrophy, *CSNB* congenital stationary night blindness, *ARB* autosomal recessive bestrophinopathy, *MIDD* maternally inherited diabetes and deafness, *ESCS* enhanced S-cone syndrome, *LORD* late-onset retinal degeneration, *LHON* leber hereditary optic neuropathy, *ADVIRC* autosomal dominant vitreoretinochoroidopathy, *NCMD* North Carolina macular dystrophy

IRD-PT module provides the user with the functionality to capture data for the specific purpose of IRDs.

Recruitment and informed consent

Both pediatric and adult patients with a genetic and/or clinical diagnosis of IRD living in Portugal and attending

Ophthalmology clinics around the country are invited to participate. Participation in the registry is voluntary. Before enrollment, the participant (patient) or their legally authorized representative must provide informed consent for the collection, storage, and use of their personal health data. No costs or compensations are involved for participants or their family members as the data collected in the IRD-PT module refers to information routinely collected by the responsible physician. All included subjects are allowed to withdraw their consent at any time, without providing a reason. This does not impact their regular follow-up at the clinic.

Ethics and regulations

The registry meets the necessary requirements for compliance with the General Data Protection Regulation (GDPR) of the European Union and all approvals were obtained prior to recruiting patients for the registry. Formal review and approval was obtained from the Portuguese Data Protection Authority (Comissão Nacional de Proteção de Dados—CNPD), HREC of Centro Hospitalar e Universitário de Coimbra (CHUC) and IRB of the Faculty of Medicine of the University of Coimbra (FMUC). All these independent entities ensured that the study protocol, governance, protections, and methods were ethical and appropriate. Furthermore, each participating core center needs to obtain approval from the respective Ethics Committee. Documentation of approval from each center is copied to the central governing office to ensure currency of approval is maintained.

All investigators (users) are mandated to sign the Investigator Declaration Form before obtaining credentials to use the registry. Both the project investigators and their institutions permit project-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but is not limited to, review by HREC and institutional governance review bodies.

Data protection

Proper handling of ethical, legal, social, and privacy issues must be a foundational component of the design, implementation, and long-term sustainability of a patient registry [7]. As part of the *retina.pt*, the IRD-PT module was designed to provide maximum data security and patient anonymity. Several well-defined procedures were put in place to protect individual patient data within the registry study. Data security, integrity, and availability is monitored and regulated.

All data transmissions between the user and the server are encrypted using 128-bit encryption (Secure Sockets Layer). The data are stored and backed up on secure servers at Portugal Telecom—Altice, TEAR 3 certified



Datacenter. Anonymity of users is also closely guarded. Individual users can only see their own data. However, users may find other centers with included data on a specific disease and ask for research collaborations within the platform. Users can withdraw their data from the registry at any time, without providing a reason.

Registry interface

Drop-down menus, pop-up explanatory notes, and tabto-jump ensures rapid and user friendly data entry. Furthermore, *retina.pt* is a web-based application that is able to run on different server operating systems. Any device with Internet access and a recent browser can be used to interact with the application. Additional software on the user's terminal is not required. When all mandatory fields have been filled, the User can "Finalize" the visit by pressing "Save". The system has been designed in such a way that it will not allow a visit to be finalized unless all the mandatory fields have been filled and all numerical data fall within prespecified ranges. Additionally, the platform allows data to be automatically filled in by third party EHR applications with identically structured information, or the possibility of the user to generate a *pdf* document that can be printed/copied to the hospital EHR system. Moreover, storage and retrieval of clinical images is possible in the patient-specific page.

Data quality

High quality data of rare diseases registries is considered to be one of the most important elements in the establishment and maintenance of a registry [20]. Quality assurance includes quality improvement activities such as medical, clinical, and record audit and observational studies, to which the ethical principles of research apply.

Interoperability

Upon the development of the *retina.pt* platform, interoperability was a key issue. First, the registry has two available languages to choose from: Portuguese and English. Second, the age-related macular degeneration (AMD)



module of *retina.pt* is already linked to the Fight Retinal Blindness! (FRB!) Project registry [2] and efforts are in place to connect it to the International Consortium for Health Outcomes Measurement (ICHOM) AMD registry. Third, the platform is serving as the eCRF for an upcoming post-market authorization clinical trial. Rare diseases are a prime example of a research area that can strongly profit from coordination on a European and international scale. To allow interoperability of the IRD-PT module with other IRD registries across the world, all the diseases are coded accordingly to ICD9, ICD10, ICD11, and ORDO (ORPHA codes) numbers. Furthermore, the genes are coded according to the OGG and MIM, and patient signs and symptoms are coded according to HPO. This is in accordance with the eye-specific dataset of the Clinical Patient Management System (CPMS) of the ERN-EYE [17]. Notably, ORDO, HPO, OGG and MIM are open-access, interoperable, community-driven, available in multiple languages and regularly updated.

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Authors' contributions

JPM conceptualized, designed and drafted the manuscript. JH and RS conceptualized and substantively revised the manuscript. ALC, JS and JNM substantively revised the manuscript. All authors have read and approved the submitted version, and have agreed both to be personally accountable for

the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Formal review and approval was obtained from the Portuguese Data Protection Authority (*Comissão Nacional de Proteção de Dados*—CNPD), Human Research Ethics Committee (HREC) of *Centro Hospitalar e Universitário de Coimbra* (CHUC) and Institutional Review Board (IRB) of the Faculty of Medicine of the University of Coimbra (FMUC). Additionally, each participating core health care provider needs to obtain approval from the respective Ethics Committee. Documentation of approval from each center is copied to the central governing office to ensure currency of approval is maintained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests in regard to this manuscript.

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