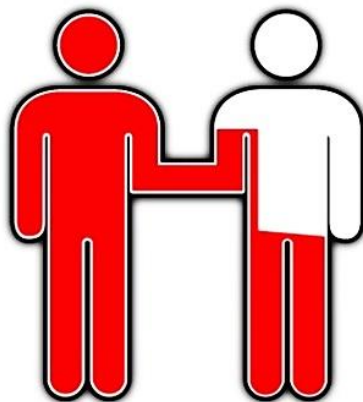


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D3.3 Progress report on global patterns of stem cell supply and demand



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Abbreviations

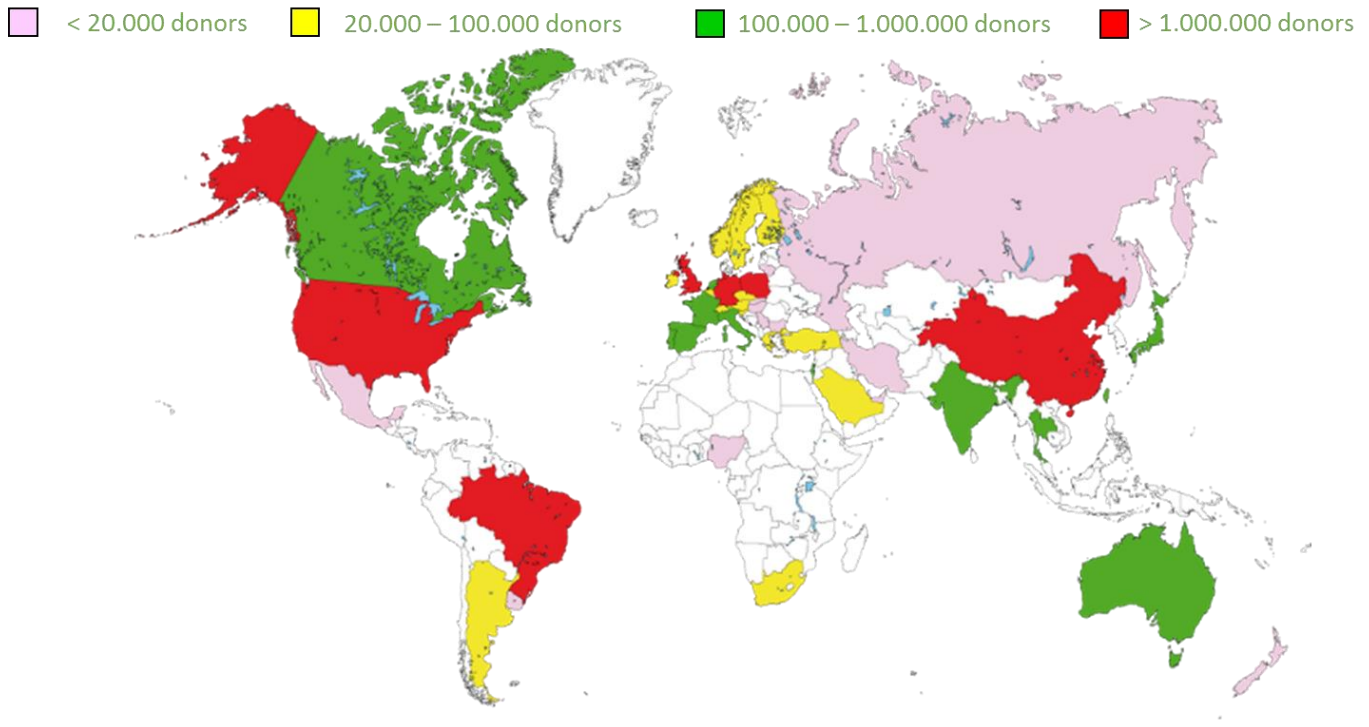
CWD	=	Common and Well-documented
IHIW	=	International HLA and Immunogenetics Workshops
HLA	=	Human Leukocyte Antigen
RUN	=	Register of Unmet Needs
WMDA	=	World Marrow Donor Association
WMDD	=	World Marrow Donor Day
WHO	=	World Health Organisation

1. Introduction to the Register of Unmet Needs

The aim of the pillar Supporting Global Development is for the member organisations to develop and grow so that more transplant patients are able to find the best possible stem cell source. This report sets out the progress made in 2018 towards supporting the WMDA community to grow and improve concerning the search for a good donor match.

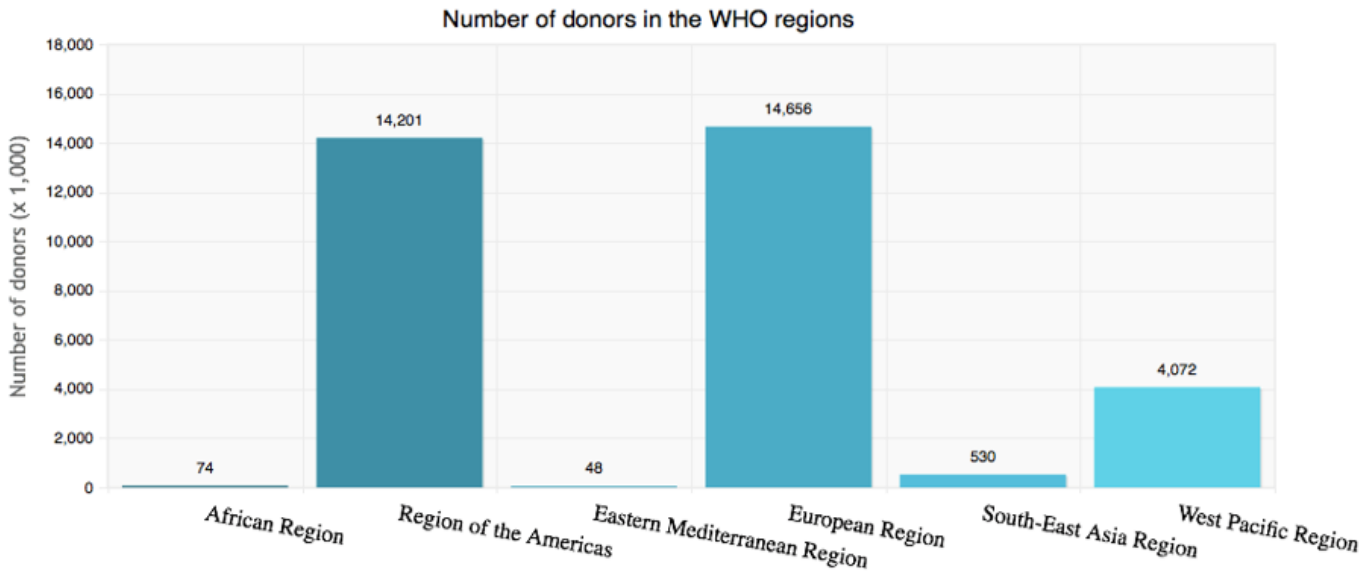
The Register of Unmet Needs (RUN) project was born in 2017 and is a new initiative that aims to identify those groups of patients that the global donor pool is currently not able to support. To help identify the gaps, all WMDA listing member organisations were asked to submit the data of their unsuccessful search cases. These cases are defined as any patient who seems to have no potential 8/8 allele matched adult donor. The Director of Bioinformatics of The National Marrow Donor Program – Be The Match (USA) has analysed the incoming information to see what patterns may arise. Donor organisations worldwide may have already a good understanding of the gaps within their own countries, but through working together as the WMDA Network, targeting those identified ethnicities across diaspora will be explored. At present, the global register contains over 33 million volunteer adult donors (Figure 1).

Figure 1. International donor register



In 2017, the distribution of these donors per World Health Organisation (WHO) region is shown in Figure 2.

Figure 2. Number of donors per WHO region



It is already clear that some of the ethnic groups desperately need more donors. While one easy answer is to recruit within the country of origin, there is an ethical dilemma whether we should build registers just for donors to be harvested knowing they could never benefit from having a transplant themselves.

Furthermore, the RUN project aims to give an exciting dimension to World Marrow Donor Day (WMDD) (Figure 3). Due to this day being celebrated every year in more than 50 countries around the world and reaching hundreds of thousands of people, it results in a great deal of media coverage. The main objective of WMDD is to thank all donors worldwide. Unrelated donors, family donors, cord blood donors, donors who have already donated and donors who are on the global registry lists waiting to donate. The secondary objective is to raise awareness among the public about being a stem cell donor and the impact of blood stem cell transplantations on patient’s lives. For many children and adults in need of a transplant it is impossible to find a match within the global register of 33 million donors and therefore more potential volunteer donors need to be recruited. This is especially true for patients with mixed race or from ethnic minorities. Fortunately, this year WMDA has noticed a growing dedication to focus on creating awareness in these populations to increase the number of mixed-race donors in the worldwide register.

Figure 3. World Marrow Donor Day



More information about WMDD can be found on the webpage <https://worldmarrowdonorday.org/>

An overview of the donor recruitment programmes and resources of 2018 is shown on the RUN website on WMDA Share.

2. Project objectives and achievements for the period

The RUN Project Group agreed on the following timeline for 2018:

Date	Task
February 2018	<ul style="list-style-type: none"> A restricted Working Area page was made in Share for the RUN Project group. Here the project group members can discuss news regarding the project and add updates. The project description, purpose and action list was added. A RUN Patient template was made in an Excel format. WMDA Listing Member Organisations were invited to fill in and submit their lost patients.
June 2018	<ul style="list-style-type: none"> An intermediate analysis was made by the Director Bioinformatics of Be The Match – The National Marrow Donor Program (USA). These results were presented at the annual WMDA Spring meeting in June in Munich. Other Listing Member Organisations were motivated to submit their data.

All WMDA listing member organisations were invited to submit data about patients from the past three years who do not have an HLA match (Figure 4). This information was treated in confidence. The aim was to analyse this pooled data for trends and to inform global recruitment strategies to address those unmet needs. Please note that only the 4 loci of HLA are marked as mandatory. The rest of the fields are optional and not necessary to fill in.

Figure 4. The RUN Patient template

ION	Country (ISO 3166-2)	Organisation										
Optional Demographics												
ID	Birth Year (YYYY)	Patient Country of Residence (ISO 3166-2)	Region (HMW/AFND region code)	Ethnicity (Haplostats codes)	Patient Ancestry (country of origin, ISO 3166-2)	Origin details (Territory, region, state, cast, other)	Patient Primary Language	A1	A2	B1	B2	
Optional HLA												
DRB3_1	DRB3_2	DRB4_1	DRB4_2	DRB5_1	DRB5_2	DQA1_1	DQA1_2	DQB1_1	DQB1_2	DPA1_1	DPA1_2	

The Listing Member Organisations that submitted their patients that they could not find an HLA match for included:

ION	Issuing Organization Name	Patients
1695	Hungarian Stem Cell Donor Registry	18
2015	Danish Stem Cell Donors - West	4
3553	NMDP-National Marrow Donor Program/Be The Match	10,344
3785	Singapore BMDP	21
4753	Czech Stem Cells Registry Prague (CSCR)	12
5440	Czech National Marrow Donor Registry Plzeň	2
6354	Anthony Nolan London	90
8118	South African Bone Marrow Registry	16
8139	Matchis Foundation	89
8261	New Zealand Bone Marrow Donor Registry	47
9738	Finnish Stem Cell Registry	79
9935	BMST India by intermediary of DKMS Registry	813

The analysed data of this collection was presented via a poster at the 12th International Donor Registry Conference (IDRC) and WMDA Working Group Meetings in June 2018 in Munich (Appendix 1).

Figure 5. Countries of Origin from patients submitted to RUN.



This map highlights the countries of origin for patients submitted to RUN (Figure 5). Clearly there is a wide range in terms of the number of patients and it is biased by the organisations submitting data.

The global demand extends beyond countries where transplant is available as a therapy and where donor registries are established.

In 2013, the catalogue of common and well-documented (CWD) HLA alleles was updated to reflect current understanding of the prevalence of specific allele sequences. CWD analysis involves validating and processing the patient HLA and then characterizing the 8 alleles at HLA-A, -B, -C and -DRB1 as being in one of three categories: common, well documented, rare.

12 organisations have provided 11,585 patients from 67 countries. HLA validation and ARD reduction resulted in:

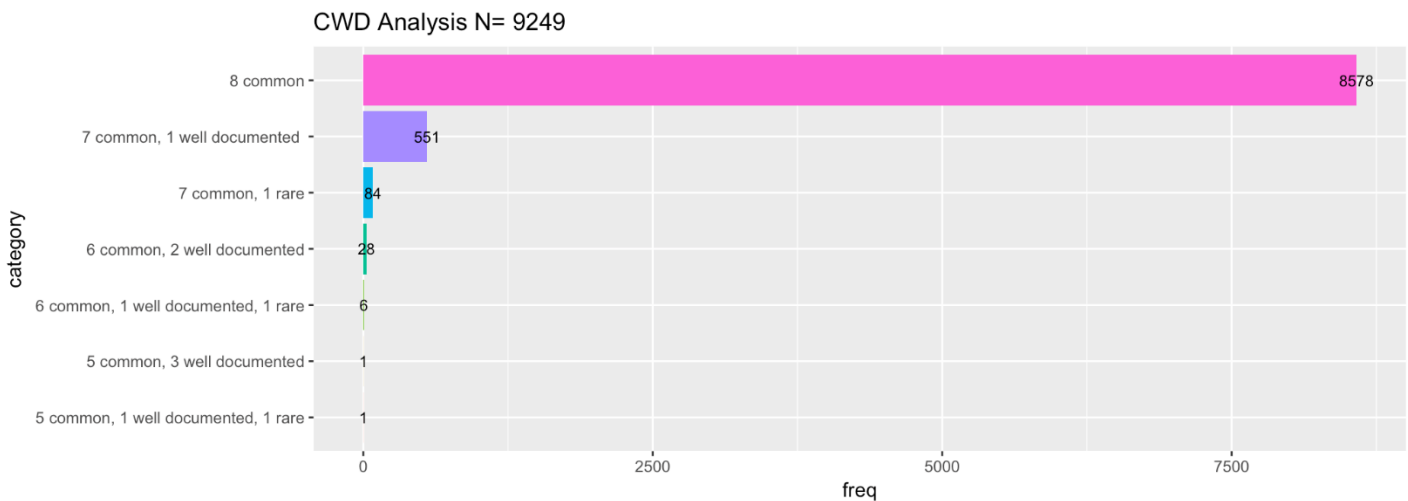
- 18 patients rejected for HLA errors
- 408 rejected for low-resolution HLA
- 1910 had ambiguity or missing loci that prevented inclusion in CWD analysis

The CWD analysis results are summarised in Figure 6:

- 93% of the patients have 8 “common” alleles
- 99% have 8 alleles that are “common” or “well documented”

This analysis demonstrates that “rare” alleles are not a factor in patients not having a match. Not finding a match is mainly due to the combination of specific alleles.

Figure 6. CWD Analysis, per category.



3. Project management

3.1 Governance and capacity building

In 2017, WMDA established a RUN Project group, made-up of volunteers from across the WMDA community, who will assist with the collection of the data of the unsuccessful cases to establish a global donor pool. They will provide support and guidance to member organisations where needed.

This group is led by the Director of Bioinformatics of The National Marrow Donor Program – Be The Match and guided by a WMDA office supporter.

3.2 Consortium management tasks and achievements

The RUN project supports the recruitment of donors from high-demand and under-represented population groups.

- The main task of the RUN Project group is to coordinate the collection of data for patients that registries could not find a matching HLA donor for. In addition, this data will regularly be pooled and analysed so the WMDA network can visualise what global patterns may emerge.
- Another task of the Project group is to gather examples of recruitment materials from different countries targeting specific population groups.

3.2.1 Changes in the consortium

There have been no changes in the consortium this year.

3.2.2 Problems and envisaged solutions

The problem that the RUN Project group encounters is that not all listing member organisations respond to the invite to submit their data for patient that they could not find correct HLA match for. The solution for this issue is to keep reminding the member organisations to upload their files.

Another dilemma is the time-consuming burden for the Director of Bioinformatics to analyse all the incoming data. Therefore, next year a workshop will be organised at the WMDA 25 year anniversary in Noordwijk (NL) to inform the organisations about using bioinformatics tools in their recruitment programmes.

3.3 Dissemination and outreach

The RUN Project group have monthly international calls, apart from the continuous email trafficking. In addition, there have been several meetings in person throughout the year, at the different WMDA congresses. Furthermore, on the WMDA Share website there is a restricted area for the RUN working group.

3.4 Communication between RUN Project group and the listing member organisations

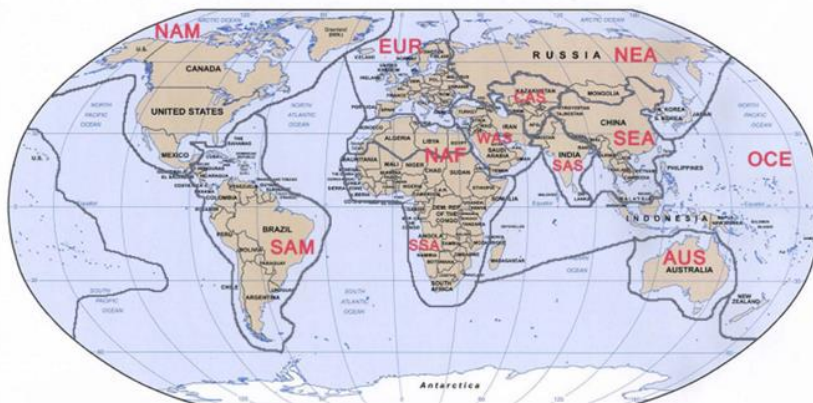
- The [RUN page](#) on WMDA Share was launched at the beginning of 2019 and includes descriptions of global patterns of stem cell supply and demand, examples of recruitments materials and FAQs. Listing member organisations can also sign up to become a project group member. In addition, the RUN patient template can be found on this page and listing member organisations are invited to submit their patients where they could not find a matching donor for.
- The WMDA listing member magazine Stem Cell Matters includes monthly updates on the RUN project.
- The WMDA members were informed about the current status of the analysed data via a poster presentation at the 12th International Donor Registry Conference (IDRC) and WMDA Working Group Meetings in June 2018 in Munich.

4. Project planning and status 2019

- The outline for the year 2019 consists of inviting and reminding more WMDA listing member organisations to submit their RUN patient templates. At the WMDA 25-year anniversary in Noordwijk (NL) the Director of Bioinformatics will host a workshop teaching WMDA member organisations to use bioinformatics tools in their recruitment programmes. This will assist with analysing the pooled data collection to get a better overview of the global patterns of stem cell supply and demand. Finally, WMDA aims for WMDD to focus even more on creating awareness for patients and donors of ethnic minorities to increase the number of mixed-race donors in the global donor register.
- It should be emphasised to pay close attention while filling in the template. In general, the Patient country is populated more often than the Patient Country of Origin. If only the Patient Country is available, then that should be used. However, if the Patient Country of Origin is accessible then that should be used. For example: in 2018, The Netherlands submitted a patient from Suriname and Finland submitted a patient from Sub-Saharan Africa.
- The RUN patient template will be updated and the standardising IHIW/AFND region code will be added. This should be completed together with the patient’s race/ethnicity.

IHIW/AFND region code

Code	Region
NAM	North America
SAM	South and Central American, and the Caribbean
EUR	Europe
NAF	North Africa
SSA	Sub-Saharan Africa
WAS	Western Asia
CAS	Central Asia
SAS	South Asia
SEA	South-East Asia
NEA	North-East Asia
OCE	Oceania
AUS	Australia



Appendix 1. Poster presentation RUN, Munich, June 2018.



RUN the Registry of Unmet Needs



Maiers M.^{1,2}, Robinett P.¹, Gragert L.^{1,2,3}, Madbouly A.^{1,2}, Schneider J.^{1,2}, Cho L.⁴, Kaur A.⁴, Eberhard H.-P.⁵, Müller C.⁵, Jörns M.⁶, van Veen C.⁶

- 1 National Marrow Donor Program/Be The Match, Minneapolis, US
- 2 Center for International Blood and Marrow Transplant Research, Minneapolis, US
- 3 Tulane University School of Medicine, Department of Pathology and Lab Medicine, NOLA, US
- 4 Singapore BMDP, Singapore, SG
- 5 Zentrales Knochenmarkspender-Register für Deutschland, Ulm, DE
- 6 World Marrow Donor Association, Leiden, NL

AIM

The Registry of Unmet Needs (RUN) is a new initiative which aims to address the needs of patients that our collective donor pool of World Marrow Donor Association (WMDA) is currently not able to serve.

We have developed data collection templates and have invited all registries to submit data about patients from the past three years **who do not have an HLA match**. Our goal is to analyze this pooled data for trends and to inform global recruitment strategies to address this unmet need.

In an effort to normalize the data we have arranged to run WMDA searches at a fixed point in time for all patients allowing a variety of definitions of match to be applied uniformly.

For example: "if the patient does not have at least one donor with a probability of 8/8 high resolution match > 75% for A, B, C, DRB1".

We anticipate that this analysis will produce specific messages that will be relevant to all registries in WMDA and can inform the messaging around "World Marrow Donor Day".

METHODS

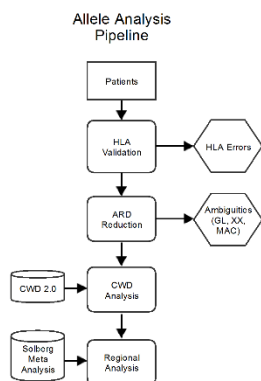
The analysis plan includes the following aspects:

1. Rare allele analysis based on the "common and well documented allele list"
2. Region analysis on the alleles using allele frequency reference data
3. Search prognosis: determination of expected genotype frequency and expected number of matches given population-specific registry sizes
4. Multi-population imputation to assign high resolution haplotypes and population identifiers to each haplotype based on haplotype frequency reference data
5. Geospatial analysis of haplotypes

In addition to patient HLA, our template includes other available patient attributes (year of birth, race/ethnicity, ancestry, specific geographical origin and language). We plan to collect family HLA data, where available, for the purpose of phasing haplotypes by segregation.

ANALYSIS

CWD analysis involves validating and processing the patient HLA and then characterizing the 8 alleles at HLA-A, -B, -C and -DRB1 as being in one of three categories: common, well documented, rare.



12 organizations has provided 11,535 patients from 67 countries.

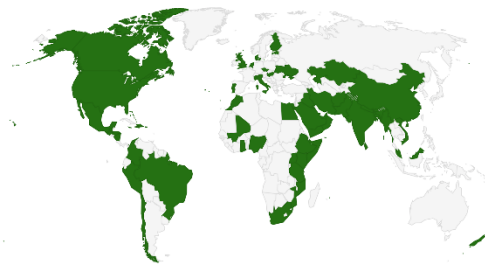
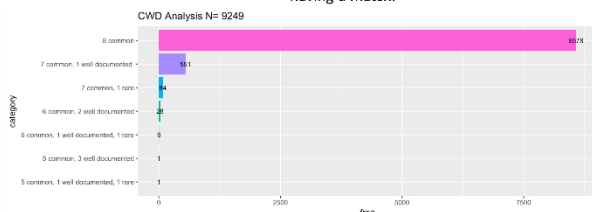
HLA validation and ARD reduction resulted in:

- 18 patients rejected for HLA errors
- 408 rejected for low-resolution HLA
- 1910 had ambiguity or missing loci that prevented inclusion in CWD analysis

The CWD analysis results are summarized in the figure below:

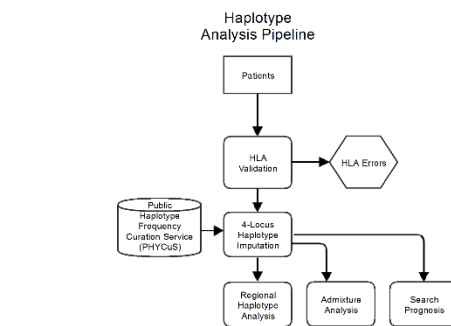
- 93% of the patients have 8 "common" alleles
- > 99% have 8 alleles that are "common" or "well documented"

This analysis demonstrates that "rare" alleles are not a factor in patients not having a match.



This map highlights the countries of origin for patients submitted to RUN. Clearly there is a wide range in terms of the number of patients and it is biased by the organizations submitting data.

The global demand extends beyond countries where transplant is available as a therapy and where donor registries are established.



ISO 3166:2	ISO name	Patients
AE	United Arab Emirates	13
AF	Afghanistan	2
AI	Anguilla	1
BD	Bangladesh	4
BM	Bermuda	2
BR	Brazil	1
BS	Bahamas	1
BT	Bhutan	1
CA	Canada	15
CL	Chile	7
CN	China	1
CN	Paracel Islands	1
CO	Colombia	2
CZ	Czech Republic	14
DK	Denmark	4
DO	Dominican Republic	1
EE	Estonia	10
EG	Egypt	1
ET	Ethiopia	1
FI	Finland	70
GB	United Kingdom of Great Britain and Northern Ireland	90
GH	Ghana	1
GT	Guatemala	1
HN	Honduras	1
HT	Haiti	1
HU	Hungary	18
IN	India	666
IQ	Iraq	1
IR	Iran, Islamic Republic of	8
IT	Italy	1
JM	Jamaica	2
KE	Kenya	4
KW	Kuwait	5
KY	Cayman Islands	1
KZ	Kazakhstan	2
LK	Sri Lanka	85
MA	Morocco	1
ML	Mali	1
MM	Myanmar	1
MU	Mauritius	1
MX	Mexico	2
MY	Malaysia	3
MZ	Mozambique	3
NG	Nigeria	5
NI	Nicaragua	1
NL	Netherlands	89
NP	Nepal	4
NZ	New Zealand	46
OM	Oman	3
PE	Peru	20
PK	Pakistan	6
PR	Puerto Rico	2
PT	Portugal	1
PT	Portugal	1
PT	Portugal	1
QA	Qatar	1
SA	Saudi Arabia	8
SG	Singapore	17
SO	Somalia	1
TZ	Tanzania, United Republic of	3
UA	Ukraine	1
UG	Uganda	3
US	United States	10,247
VI	Virgin Islands, U.S.	1
VN	Vietnam	1
YE	Yemen	3
ZA	South Africa	17

RESOURCES

RUN Analysis Pipeline

<https://github.com/mmaiernmmdp/RUN>

pyARD: Python library for Antigen Recognition Domain analysis

<https://github.com/nmdp-bioinformatics/pyARD>

Public Haplotype Frequency Curation Service

<https://github.com/nmdp-bioinformatics/service-haplotype-frequency-curation>

CWD 2.0

doi: 10.1111/tan.12093

Solberg Meta Analysis

doi:10.1016/j.humimm.2008.05.001