European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

VASCERN (March 2018-February 2019) – CONTINUOUS REPORTING

Work Package 6 – Clinical trials and Research

Deliverable 6.1 – Clinical trials

Co-funded by the Health Programme of the European Union

Objective

VASCERN aims to promote European cooperation for scientific research and clinical trials. We collect information within the Rare Disease Working Groups (RDWGs) about research project ongoing and perform a bibliographical research in order to report on research publications involving members from our 31 HCPs. We also publish and disseminate information about the calls for research projects, for instance, the European Joint Programme on Rare Diseases Research (EJP-RD) calls.

Objective: reinforce research in rare vascular diseases

Target: Launch one clinical trial within VASCERN

Outcome/impact Indicators: Improved research/publication in peer review journal.

Implementation

The following lists of activity in clinical trials and research projects are divided into the 5 Rare Disease Working Groups (RDWGs). Please note that the following lists of clinical trials, research studies and publications may not be exhaustive for each RDWG.

Hereditary Haemorrhagic Telangiectasia Working Group (HHT-WG):

6A) MULTI ERN CLINICAL TRIALS AND RESEARCH

6A1. Collaborative clinical trials (6+ ERNs)

MAGER (NL), BUSCARINI (I), DUPUIS GIROD (F) KJELDSEN (DK), SABBA (I), SHOVLIN (UK)
Principle Investigator Dr. Erwin J.M. van Geenen, Radboudumc, Nijmegen, Netherlands
Effectiveness of Somatostatin Analogues in Patients with hereditary hemorrhagic telangiectasia and symptomatic gastrointestinal bleeding,
the SAIPAN-trial: a multicenter, randomized, open-label, parallel-group, superiority trial
Project funded late 2018, and now in set up (Ethical applications in progress)

6A2. Collaborative research studies

6A2.1:
BUSCARINI (I), KJELDSEN (DK), MAGER (NL), SUPPRESSA (P) DUPUIS GIROD (F) SHOVLIN (UK), and other VASCERN HHT members and collaborators:
VASCERN HHT DRUG REGISTRY
First manuscript published Feb 2019 (see 6A3.3 below)

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6A2.2
SHOVLIN (UK) KJELDSEN (DK), MAGER (NL), SUPPRESSA (P) DUPUIS GIROD (F) BUSCARINI (I), and other VASCERN HHT members and collaborators:
New oral anticoagulants in patients with hereditary hemorrhagic telangiectasia.
Research completed. Manuscript in final stages of preparation Feb 2019

6A2.3
SHOVLIN (UK), DUPUIS GIROD (F) BUSCARINI (I), MAGER (NL), KJELDSEN (DK), BOTELLA (E) AND THE HHT GECIP SUBDOMAIN:
HHT IN THE 100,000 GENOMES PROJECT (ongoing)

6A3 Collaborative publications (March 2018-February 2019):

6A3.1
Shovlin CL, Buscarini E, Kjeldsen AD, Mager HJ, Sabba C, Droege F, Geisthoff U, Ugolini S, Dupuis-Girod S
European Reference Network For Rare Vascular Diseases (VASCERN) Outcome Measures For Hereditary Haemorrhagic Telangiectasia (HHT).
Orphanet J Rare Dis. 2018 Aug 15;13(1):136. doi: 10.1186/s13023-018-0850-2.

6A3.2
Shovlin C, Bamford K, Sabbà C, Mager HJ, Kjeldsen A, Droege F, Buscarini E, Dupuis-Girod S; VASCERN HHT.
Prevention of serious infections in hereditary hemorrhagic telangiectasia: roles for prophylactic antibiotics, the pulmonary capillaries-but not vaccination.
Haematologica. 2019 Feb;104(2):e85-e86. doi: 10.3324/haematol.2018.209791.

6A3.3
Buscarini E, Botella LM, Geisthoff U, Kjeldsen AD, Mager HJ, Pagella F, Suppressa P, Zarrabeitia R, Dupuis-Girod S, Shovlin CL; VASCERN-HHT.
Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia.
Orphanet J Rare Dis. 2019 Feb 4;14(1):28. doi: 10.1186/s13023-018-0982-4. PMID: 30717761

6A3.4
Claire SHOVLIN (UK), Saverio ALICANTE (Italy), Luisa BOTELLA (Spain), Nicky COOTE (UK), Claudia CROCIONE (Italy), Freya DROEGE (Germany), Didier ERASME (France), Anette KJELDSEN (Denmark), David LEFROY (UK), Gennaro Mariano LENATO (Italy), Hans-Jurgen MAGER (The Netherlands), Marco POST (The Netherlands), Carlo SABBÀ (Italy), Patrizia SUPPRESSA (Italy) ; Ulrich SURE (Germany), Pernille TØRRING (Denmark), Sara UGOLINI (Italy), Elisabetta BUSCARINI (Italy)*, and Sophie DUPUIS-GIROD (France)* Hereditary Haemorrhagic Telangiectasia. Orphanet Encyclopedia for Professionals
(Methodological notes provided at https://vascern.eu/orphanet-text-on-hht-updated-by-the-vascern-hht-wg/)

6A3.5 VASCERN DO'S AND DON'TS FACTSHEETS FOR RARE VASCULAR DISEASE PATIENTS FACING FREQUENT SITUATIONS: https://vascern.eu/wp-content/uploads/2018/09/Fiches_Hereditary-Haemorrhagic-Telangiectasia_FINAL-web.pdf

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6A3.6

Characterization of a mutation in the zona pellucida module of Endoglin that causes Hereditary Hemorrhagic Telangiectasia.Ruiz-Llorente L, Chiapparino E, Plumitallo S, Danesino C, Bayrak-Toydemir P, **Pagella F, Manfredi G**, Bernabeu C, Jovine L, Olivieri C.Gene. 2019 Feb 11;696:33-39. doi: 10.1016/j.gene.2019.02.016. [Epub ahead of print]PMID: 30763665

6B) SINGLE ERN CLINICAL TRIALS AND RESEARCH

6B1. Clinical trials and Research projects ongoing within the RDWG (individual HCPs:

Multiple (> 20) research projects are currently ongoing in individual HHT WG HCPs, with currently no second HHT WG HCP participating. These will continue to be developed in Year 3.

6B2 HCP individual publications (March 2018-February 2019):

The following list of publications is not exhaustive. We have included the most relevant publications to include in this report and do not repeat the jpint publications listed above

1) **Hammersmith Hospital, Imperial College Healthcare NHS Trust, UK:**

Gawecki F, Strangeways T, Amin A, Perks J, Wolfenden H, Thurainatnam S, Rizvi A, Jackson JE, Santhirapala V, Myers J, Brown J, Howard LSGE, Tighe HC, **Shovlin CL** Exercise capacity reflects airflow limitation rather than hypoxaemia in patients with pulmonary arteriovenous malformations.QJM. 2019 Jan 17. doi: 10.1093/qjmed/hcz023. [Epub ahead of print]PMID:30657990

Fatania G, Gilson C, Glover A, Alsafi A, Jackson JE, Patel MC, **Shovlin CL**. Uptake and radiological findings of screening cerebral magnetic resonance scans in patients with hereditary haemorrhagic telangiectasia. Intractable Rare Dis Res. 2018 Nov;7(4):236-244. doi: 10.5582/irdr.2018.01103.PMID: 30560015

Thielemans L, Layton DM, **Shovlin CL**. Low serum haptoglobin and blood films suggest intravascular haemolysis contributes to severe anaemia in hereditary haemorrhagic telangiectasia. Haematologica. 2018 Oct 18. pii: haematol.2018.205682. doi: 10.3324/haematol.2018.205682. [Epub ahead of print]

J Vasc Interv Radiol. 2018 Sep;29(9):1313-1315. doi: 10.1016/j.jvir.2017.12.016. Acquired Transpleural Systemic Artery-to-Pulmonary Artery Communication Mimicking a Pulmonary Arteriovenous Malformation and Causing a False-Positive Diagnosis of a Pulmonary Embolus. Alsafi A, **Shovlin CL**, Jackson JE.

Plus 5 in 6A3

2) **CHU de Lyon HCL, France**

Eur J Hum Genet. 2019 Feb 1. doi: 10.1038/s41431-018-0332-y. [Epub ahead of print]Exome sequencing in clinical settings: preferences and experiences of parents of children with rare diseases (SEQUAPRE study).Chassagne A1, Pélissier A, Houdayer F, Cretin E, Gautier E, Salvi D, Kidri S, Godard A, Thauvin-Robinet C, Masurel A, Lehalle D, Jean-Marçais N, Thevenon J, Lesca G, Putoux A5, Cordier MP, **Dupuis-Girod S**, Till M, Duffourd Y, Rivière JB, Joly L, Juif C, Putois O, Ancet P,

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Lapointe AS, Morin P, Edery P, Rossi M, Sanlaville D, Béjean S, Peyron C, Faivre L10,11. PMID: 30710147

Recurrence of hereditary hemorrhagic telangiectasia after liver transplantation: clinical implications and physiopathological insights.Dumortier J, **Dupuis-Girod S,** Valette PJ, Valent A, Guillaud O, Saurin JC, Hervieu V, Robinson P, Plauchu H, Paliard P, Boillot O, Scoazec JY.Hepatology. 2018 Dec 14. doi: 10.1002/hep.30424. [Epub ahead of print]PMID: 30549294

Hyperammonemic encephalopathy associated with hereditary hemorrhagic telangiectasia. Dumortier J, Guillaud O, Erard-Poinsot D, D**upuis-Girod S**, Francoz C, Durand F.Clin Res Hepatol Gastroenterol. 2018 Nov 14. pii: S2210-7401(18)30227-4. doi: 10.1016/j.clinre.2018.10.011. [Epub ahead of print] No abstract available.PMID: 30447907

12q13.12q13.13 microdeletion encompassing ACVRL1 and SCN8A genes: Clinical report of a new contiguous gene syndrome. Poisson A, Lesca G, Chatron N, Favre E, Cottin V, Gamondes D, Sanlaville D, Edery P, Giraud S, Demily C, **Dupuis-Girod S**. Eur J Med Genet. 2018 Oct 30. pii: S1769-7212(18)30557-3. doi: 10.1016/j.ejmg.2018.10.017. [Epub ahead of print]PMID: 30389587

Pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia: Correlations between computed tomography findings and cerebral complications.Etievant J, Si-Mohamed S, Vinurel N, **Dupuis-Girod S**, Decullier E, Gamondes D, Khouatra C, Cottin V, Revel D.Eur Radiol. 2018 Mar;28(3):1338-1344. doi: 10.1007/s00330-017-5047-x. Epub 2017 Oct 10. PMID: 29018941

Plus 5 in 6A3

3) **Maggiore Hospital, ASST Crema, Italy**

Liver involvement in hereditary hemorrhagic telangiectasia.**Buscarini E,** Gandolfi S, **Alicante S,** Londoni C, **Manfredi G**.Abdom Radiol (NY). 2018 Jul 10. doi: 10.1007/s00261-018-1671-4. [Epub ahead of print]PMID: 29987403

Ultrasonography in Liver Vascular Disease.De Gottardi A, Berzigotti A, **Buscarini E**, García Criado A.Ultraschall Med. 2018 Aug;39(4):382-405. doi: 10.1055/a-0647-1658. Epub 2018 Aug 2.PMID: 30071557

Plus 6 in 6A3

4) **Odense University Hospital, Denmark:**

Comorbidity among HHT patients and their controls in a 20 years follow-up period. Aagaard KS, **Kjeldsen AD, Tørring PM**, Green A. Orphanet J Rare Dis. 2018 Dec 14;13(1):223. doi: 10.1186/s13023-018-0962-8. PMID: 30547819

Pulmonary arteriovenous malformations: a radiological and clinical investigation of 136 patients with long-term follow-up. Andersen PE, **Tørring PM**, Duvnjak S, Gerke O, Nissen H**, Kjeldsen AD**.Clin Radiol. 2018 Nov;73(11):951-957. doi: 10.1016/j.crad.2018.07.096. Epub 2018 Aug 4. PMID: 30086858

Plus 5 in 6A3

5) **Essen University Hospital, Germany:**

Life expectancy and comorbidities in patients with hereditary hemorrhagic telangiectasia. **Droege F**, Thangavelu K, Stuck BA, Stang A, Lang S**, Geisthoff U**. Vasc Med. 2018 Aug;23(4):377-383. doi: 10.1177/1358863X18767761. Epub 2018 May 20.PMID: 29781402

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Treatment with low-dose tacrolimus inhibits bleeding complications in a patient with hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension. Sommer N, **Droege F**, Gamen KE, **Geisthoff U**, Gall H, Tello K, Richter MJ, Deubner LM, Schmiedel R, Hecker M, Spiekerkoetter E, Wirsching K, Seeger W, Ghofrani HA, Pullamsetti S. Pulm Circ. 2019 Apr-Jun;9(2):2045894018805406. doi: 10.1177/2045894018805406. Epub 2018 Sep 27.PMID: 30260738

Nasal self-packing for epistaxis in Hereditary Hemorrhagic Telangiectasia increases quality of life. **Droege F**, Lueb C, Thangavelu K, Stuck BA, Lang S, **Geisthoff U**. Rhinology. 2019 Feb 10. doi: 10.4193/Rhin18.141.

Plus 6A3

6) **Fondazione IRCCS Policlinico San Matteo, Pavia, Italy:**

Different forms of pulmonary hypertension in a family with clinical and genetic evidence for hereditary hemorrhagic teleangectasia type 2.Greco A, Plumitallo S, Scelsi L, Maggi G, Sobrero M, Turco A, Raineri C, Arseni N, Cappelletti D, Visconti LO, **Pagella F**, Spinozzi G, Ghio S, Olivieri C, Danesino C.Pulm Circ. 2018 Oct-Dec;8(4):2045894018782664. doi: 10.1177/2045894018782664. Epub 2018 May 25.PMID: 29799317

Plus 6A3

7) **AziendaOspedaliero-UniversitariaConsorziale di Bari Policlinico-Giovanni XXIII, Italy**

No HHT-related publications from March 2018-February 2019

Plus 6A3

8) **St. Antonius Hospital, Nieuwegein, The Netherlands**

Systematic screening in hereditary hemorrhagic telangiectasia: a review.Kroon S, Snijder RJ, Faughnan ME, **Mager HJ**.Curr Opin Pulm Med. 2018 May;24(3):260-268. doi: 10.1097/MCP.0000000000000472.PMID: 29470256

Pulmonary Arterial Hypertension and Hereditary Haemorrhagic Telangiectasia. Vorselaars VMM, Hosman AE, Westermann CJJ, Snijder RJ, Mager JJ, Goumans MJ, Post MC. Int J Mol Sci. 2018 Oct 17;19(10). pii: E3203. doi: 10.3390/ijms19103203. Review. PMID: 30336550

Association of common candidate variants with vascular malformations and intracranial hemorrhage in hereditary hemorrhagic telangiectasia. Pawlikowska L, Nelson J, Guo DE, McCulloch CE, Lawton MT, Kim H, Faughnan ME; Brain Vascular Malformation Consortium HHT Investigator Group. Mol Genet Genomic Med. 2018 May;6(3):350-356. doi: 10.1002/mgg3.377. Epub 2018 Mar 6. PMID: 29932521

Reproducibility of right-to-left shunt quantification using transthoracic contrast echocardiography in hereditary haemorrhagic telangiectasia. Vorselaars VMM, Velthuis S, Huitema MP, Hosman AE, Westermann CJJ, Snijder RJ, Mager JJ, Post MC. Neth Heart J. 2018 Apr;26(4):203-209. doi: 10.1007/s12471-018-1094-4. PMID: 29497946

Plus 6A3

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Heritable Thoracic Aortic Disease Working Group (HTAD-WG):

Clinical trials:

The HTAD-WG does not have any clinical trials underway at the moment as they have chosen to focus on other work packages such as patient pathways and clinical guidelines. They have however been very busy with research studies and have authored many scientific publications.
A Resveratrol trial in adult Marfan patients is currently in its initial phases and will involve two HCPs from the HTAD WG, Academic Medical Center (NL), Radboud University Medical Center (NL).

Research projects ongoing within the RDWG (with several HCP members):

ROPAC III registry; organized by the European Society of Cardiology, that will follow pregnant women with thoracic aortic diseases, is currently in the development phase (the Case Report Forms are being prepared) but the inclusion of patients could start as early as in May-June 2018. Both our coordinator Prof Guillaume Jondeau (Hôpital Bichat (FR)) and HTAD-WG Chair, Prof Julie De Backer (Ghent University (BE)) are executive committee members of this registry.
Montalcino Aortic Consortium (MAC) registry; which is an international registry on HTADs, with the European part of the project centralized in Paris, and that involves numerous HCP representatives from the HTAD-WG including those from Ghent University (BE), Hôpital Bichat (FR), University Medical Center Hamburg-Eppendorf (DE), Semmelweis University (HU), Academic Medical Center (Netherlands), IRCCS Foundation Policlino San Matteo (IT) and Azienda Socio Sanitaria Territoriale Fatebenefratelli - Sacco (IT).
The Rotterdam Bicuspid Aortic Valve (BAV) study, together with Radboud University Medical Center (NL) and University of Antwerp (BE).
Marfan cardiomyopathy study; with collaboration between Ghent University (BE) and Semmelweis University (HU).

Research projects ongoing within the RDWG (individual HCPs):

There are various research projects currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (March 2018 –February 2019):

SMAD3 pathogenic variants: risk for thoracic aortic disease and associated complications from the Montalcino Aortic Consortium. Hostetler EM, Regalado ES, Guo DC, Hanna N, Arnaud P, Muiño-Mosquera L, Callewaert BL, Lee K, Leal SM, Wallace SE, Rideout AL, Dyack S, Aatre RD, **Boileau C, De Backer J, Jondeau G,** Milewicz DM.J Med Genet. 2019 Jan 19. pii: jmedgenet-2018-105583. doi: 10.1136/jmedgenet-2018-105583. [Epub ahead of print] PMID: 30661052

Hungarian Marfan family with large FBN1 deletion calls attention to copy number variation detection in the current NGS era. **Benke K,** Ágg B, Meienberg J, Kopps AM, Fattorini N, Stengl R, Daradics N, Pólos M, Bors A, Radovits T, Merkely B, **De Backer J**, **Szabolcs Z**, Mátyás G.J Thorac Dis. 2018 Apr;10(4):2456-2460. doi: 10.21037/jtd.2018.04.40. PMID: 29850152

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Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysm and Dissection.Renard M, Francis C, Ghosh R, Scott AF, Witmer PD, Adès LC, Andelfinger GU, Arnaud P, **Boileau C,** Callewaert BL, Guo D, Hanna N, Lindsay ME, Morisaki H, Morisaki T, Pachter N, **Robert L**, **Van Laer L**, Dietz HC, **Loeys BL**, Milewicz DM, **De Backer J**. J Am Coll Cardiol. 2018 Aug 7;72(6):605-615. doi: 10.1016/j.jacc.2018.04.089.PMID: 30071989

Expert consensus recommendations on the cardiogenetic care for patients with thoracic aortic disease and their first-degree relatives.Verhagen JMA, Kempers M, Cozijnsen L, Bouma BJ, Duijnhouwer AL, Post JG, Hilhorst-Hofstee Y, Bekkers SCAM, Kerstjens-Frederikse WS, van Brakel TJ, Lambermon E, Wessels MW, Loeys BL, Roos-Hesselink JW, van de Laar IMBH; National Working Group on BAV & TAA. Int J Cardiol. 2018 May 1;258:243-248. doi: 10.1016/j.ijcard.2018.01.145. Epub 2018 Feb 7. Review. PMID: 29452988

Results of next-generation sequencing gene panel diagnostics including copy-number variation analysis in 810 patients suspected of heritable thoracic aortic disorders. Overwater E, Marsili L, Baars MJH, Baas AF, van de Beek I, Dulfer E, van Hagen JM, Hilhorst-Hofstee Y, **Kempers M**, Krapels IP, Menke LA, Verhagen JMA, Yeung KK, Zwijnenburg PJG, **Groenink M**, van Rijn P, Weiss MM, Voorhoeve E, van Tintelen JP, Houweling AC, Maugeri A.Hum Mutat. 2018 Sep;39(9):1173-1192. doi: 10.1002/humu.23565. Epub 2018 Jul 12.

Novel pathogenic SMAD2 variants in five families with arterial aneurysm and dissection: further delineation of the phenotype.Cannaerts E**, Kempers M**, Maugeri A, Marcelis C, Gardeitchik T, Richer J, Micha D, Beauchesne L, **Timmermans J**, Vermeersch P, Meyten N, Chénier S, van de Beek G, Peeters N, Alaerts M, Schepers D, Van Laer L, Verstraeten A**, Loeys B.**J Med Genet. 2018 Jul 2. pii: jmedgenet-2018-105304. doi: 10.1136/jmedgenet-2018-105304. [Epub ahead of print]PMID: 29967133

A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3.Schepers D, Tortora G, Morisaki H, MacCarrick G, Lindsay M, Liang D, Mehta SG, Hague J, Verhagen J, **van de Laar I**, **Wessels M**, Detisch Y, van Haelst M, Baas A, Lichtenbelt K, Braun K, van der Linde D, Roos-Hesselink J, McGillivray G, Meester J, Maystadt I, Coucke P, El-Khoury E, Parkash S, Diness B, Risom L, Scurr I, Hilhorst-Hofstee Y, Morisaki T, Richer J, Désir J, **Kempers M**, Rideout AL, Horne G, Bennett C, Rahikkala E, Vandeweyer G, Alaerts M, **Verstraeten A**, Dietz H, Van Laer L, **Loeys B**. Hum Mutat. 2018 May;39(5):621-634. doi: 10.1002/humu.23407. Epub 2018 Mar 6. PMID: 29392890

HCP individual publications (March 2018 –February 2019):

1) **Center for Medical Genetics Ghent, Ghent University, Ghent, Belgium:**

Looking for the Missing Links: Challenges in the Search for Genotype-Phenotype Correlation in Marfan Syndrome. De Backer J, Campens L, Muiño Mosquera L. Circ Genom Precis Med. 2018 Jun;11(6):e002185. doi: 10.1161/CIRCGEN.118.002185. No abstract available.PMID: 29848616

Tailoring the American College of Medical Genetics and Genomics and the Association for Molecular Pathology Guidelines for the Interpretation of Sequenced Variants in the FBN1 Gene for Marfan Syndrome: Proposal for a Disease- and Gene-Specific Guideline. Muiño-Mosquera L, Steijns F, Audenaert T, Meerschaut I, De Paepe A, Steyaert W, Symoens S, Coucke P, Callewaert B, Renard M, De Backer J. Circ Genom Precis Med. 2018 Jun;11(6):e002039. doi: 10.1161/CIRCGEN.117.002039.PMID: 29875124

A heart for fibrillin: spatial arrangement in adult wild-type murine myocardial tissue. Steijns F, van Hengel J, Sips P, De Backer J, Renard M. Histochem Cell Biol. 2018 Jun 20. doi: 10.1007/s00418-018-1686-5. [Epub ahead of print] PMID: 29926163

Heart failure and sudden cardiac death in heritable thoracic aortic disease caused by pathogenic variants in the SMAD3 gene. **Backer J**, Braverman AC.Mol Genet Genomic Med. 2018 May 1. doi: 10.1002/mgg3.396. [Epub ahead of print]PMID: 29717556

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Influence of Aortic Stiffness on Aortic-Root Growth Rate and Outcome in Patients With the Marfan Syndrome. Selamet Tierney ES, Levine JC, Sleeper LA, Roman MJ, Bradley TJ, Colan SD, Chen S, Campbell MJ, Cohen MS, **De Backer J**, Heydarian H, Hoskoppal A, Lai WW, Liou A, Marcus E, Nutting A, Olson AK, Parra DA, Pearson GD, Pierpont ME, Printz BF, Pyeritz RE, Ravekes W, Sharkey AM, Srivastava S, Young L, Lacro RV; Pediatric Heart Network Investigators. Am J Cardiol. 2018 May 1;121(9):1094-1101. doi: 10.1016/j.amjcard.2018.01.016. Epub 2018 Feb 13. PMID: 29631804

2) **Centre national de Référence pour le Syndrome de Marfan et apparentés, Hôpital Bichat-Claude Bernard, APHP, Paris**

AVIATOR: An open international registry to evaluate medical and surgical outcomes of aortic valve insufficiency and ascending aorta aneurysm. de Heer F, Kluin J, Elkhoury G, **Jondeau G**, Enriquez-Sarano M, Schäfers HJ, Takkenberg JJM, Lansac E; Aortic Valve Repair Research Network Investigators. J Thorac Cardiovasc Surg. 2018 Oct 26. pii: S0022-5223(18)32849-6. doi: 10.1016/j.jtcvs.2018.10.076. [Epub ahead of print]PMID: 30553597

Risk of Ascending Aortic Aneurysm in Patients With Autosomal Dominant Polycystic Kidney Disease. Bouleti C, Flamant M, Escoubet B, Arnoult F, **Milleron O**, Vidal-Petiot E, Langeois M, Ou P, Vrtovsnik F, **Jondeau G**. Am J Cardiol. 2019 Feb 1;123(3):482-488. doi: 10.1016/j.amjcard.2018.10.030. Epub 2018 Nov 6. PMID: 30477801

High prevalence of ventricular repolarization abnormalities in people carrying TGFβR2 mutations. Extramiana F, **Milleron O,** Elbitar S, Uccellini A, Langeois M, Spentchian M, Delorme G, Arnoult F, Denjoy I, Bouleti C, Fressart V, Iserin F, Maison-Blanche P, Abifadel M, Leenhardt A, Boileau C, **Jondeau G**. Sci Rep. 2018 Aug 29;8(1):13019. doi: 10.1038/s41598-018-31298-5. PMID: 30158670

Marfan Syndrome Variability: Investigation of the Roles of Sarcolipin and Calcium as Potential Transregulator of FBN1 Expression. Benarroch L, Aubart M, Gross MS, Jacob MP, Arnaud P, Hanna N, **Jondeau G, Boileau C**. Genes (Basel). 2018 Aug 21;9(9). pii: E421. doi: 10.3390/genes9090421. PMID: 30134586

Association of modifiers and other genetic factors explain Marfan syndrome clinical variability. Aubart M, Gazal S, Arnaud P, Benarroch L, Gross MS, Buratti J, Boland A, Meyer V, Zouali H, Hanna N, **Milleron O**, Stheneur C, Bourgeron T, Desguerre I, Jacob MP, Gouya L, Génin E, Deleuze JF, **Jondeau G, Boileau C.** Eur J Hum Genet. 2018 Dec;26(12):1759-1772. doi: 10.1038/s41431-018-0164-9. Epub 2018 Aug 7. PMID: 30087447

MYLK pathogenic variants aortic disease presentation, pregnancy risk, and characterization of pathogenic missense variants.Wallace SE, Regalado ES, Gong L, Janda AL, Guo DC, Russo CF, Kulmacz RJ, Hanna N, **Jondeau G, Boileau C**, Arnaud P, Lee K, Leal SM, Hannuksela M, Carlberg B, Johnston T, Antolik C, Hostetler EM, Colombo R, Milewicz DM. Genet Med. 2019 Jan;21(1):144-151. doi: 10.1038/s41436-018-0038-0. Epub 2018 Jun 20. PMID: 29925964

From genetics to response to injury: vascular smooth muscle cells in aneurysms and dissections of the ascending aorta. Michel JB, **Jondeau G**, Milewicz DM. Cardiovasc Res. 2018 Mar 15;114(4):578-589. doi: 10.1093/cvr/cvy006. PMID: 29360940

3) **University Hospital of Antwerp, Belgium**

ROBO4 variants predispose individuals to bicuspid aortic valve and thoracic aortic aneurysm.Gould RA, Aziz H, Woods CE, Seman-Senderos MA, Sparks E, Preuss C, Wünnemann F, Bedja D, Moats CR, McClymont SA, Rose R, Sobreira N, Ling H, MacCarrick G, Kumar AA, Luyckx I, Cannaerts E, Verstraeten A, Björk HM, Lehsau AC, Jaskula-Ranga V, Lauridsen H, Shah AA, Bennett CL, Ellinor PT, Lin H, Isselbacher EM, Lino Cardenas CL, Butcher JT, Hughes GC, Lindsay ME; Baylor-Hopkins Center for Mendelian Genomics; MIBAVA Leducq Consortium, Mertens L, Franco-Cereceda A,

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Verhagen JMA, Wessels M, Mohamed SA, Eriksson P, Mital S, Van Laer L, **Loeys** BL, Andelfinger G, McCallion AS, Dietz HC. Nat Genet. 2019 Jan;51(1):42-50. doi: 10.1038/s41588-018-0265-y. Epub 2018 Nov 19. PMID: 30455415

Aortic aneurysm: An underestimated serious finding in the EP300 mutation phenotypical spectrum.Luyckx I, Bolar N, Diness BR, Hove HB, Verstraeten A, **Loeys BL**. Eur J Med Genet. 2019 Feb;62(2):96. doi: 10.1016/j.ejmg.2018.06.008. Epub 2018 Jun 12. No abstract available.PMID: 29906517

Loeys-Dietz Syndrome.**Loeys BL**, Dietz HC. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2008 Feb 28 [updated 2018 Mar 1].PMID: 20301312

4) **University Medical Center Hamburg-Eppendorf, Germany**

Next-generation sequencing of 32 genes associated with hereditary aortopathies and related disorders of connective tissue in a cohort of 199 patients.Renner S, Schüler H, Alawi M, Kolbe V, Rybczynski M, Woitschach R, Sheikhzadeh S, Stark VC, Olfe J, Roser E, Seggewies FS, Mahlmann A, Hempel M, Hartmann MJ, Hillebrand M, Wieczorek D, Volk AE, Kloth K, Koch-Hogrebe M, Abou Jamra R, Mitter D, Altmüller J, Wey-Fabrizius A, Petersen C, Rau I, Borck G, Kubisch C, Mir TS, **von Kodolitsch Y**, Kutsche K, Rosenberger G.Genet Med. 2019 Jan 24. doi: 10.1038/s41436-019-0435-z. [Epub ahead of print] PMID: 30675029

Emergency Use of Branched Thoracic Endovascular Repair in the Treatment of Aortic Arch Pathologies.Law Y, Kölbel T, Detter C, Rohlffs F, **von Kodolitsch Y**, Makaloski V, Debus ES, Tsilimparis N.Ann Thorac Surg. 2018 Oct 30. pii: S0003-4975(18)31535-2. doi: 10.1016/j.athoracsur.2018.09.020. [Epub ahead of print]PMID: 30389447

Does statin therapy impact the proximal aortopathy in aortic valve disease? Sequeira Gross T, Naito S, Neumann N, Petersen J, Kuntze T, Reichenspurner H, **von Kodolitsch Y**, Girdauskas E.QJM. 2018 Sep 1;111(9):623-628. doi: 10.1093/qjmed/hcy129.PMID: 29917097

Branched endografts in the aortic arch following open repair for DeBakey Type I aortic dissection. Tsilimparis N, Detter C, Heidemann F, Spanos K, Rohlffs F, von Kodolitsch Y, Debus SE, Kölbel T.Eur J Cardiothorac Surg. 2018 Sep 1;54(3):517-523. doi: 10.1093/ejcts/ezy133.PMID: 29608660

Ocular manifestation in Marfan syndrome: corneal biomechanical properties relate to increased systemic score points. Scheibenberger D, Frings A, Steinberg J, Schüler H, Druchkiv V, Katz T, von Kodolitsch Y, Linke S. Graefes Arch Clin Exp Ophthalmol. 2018 Jun;256(6):1159-1163. doi: 10.1007/s00417-018-3946-4. Epub 2018 Mar 10.PMID: 29525839

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5) **Semmelweis University, Budapest, Hungary**

No additional individual HTAD-related publications in 2017 (see collaborative publications, above).

6) **IRCCS Foundation Policlino San Matteo, Italy**

Thoracoscopic Treatment of Pneumothorax in Marfan Syndrome: Hemostatic Patch to Support Lung Resection Recovery.Pelizzo G**, Arbustini E**, Pasqua N, Morbini P, Calcaterra V.Case Rep Surg. 2018 Sep 4;2018:7597215. doi: 10.1155/2018/7597215. eCollection 2018.PMID: 30254783

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When Genes, More Than Phenotype, Identify Different Diseases: The Case of Nonsyndromic HTAA/D. **Arbustini E**, Giuliani L, Di Toro A. J Am Coll Cardiol. 2018 Aug 7;72(6):616-619. doi: 10.1016/j.jacc.2018.03.547. No abstract available. PMID: 30071990

Common presentation of rare diseases: Aortic aneurysms & valves. Arbustini E, Favalli V, **Di Toro A,** Giuliani L, Limongelli G.Int J Cardiol. 2018 Apr 15;257:358-365. doi: 10.1016/j.ijcard.2018.01.003. Review. PMID: 29506732

7) **Careggi Hospital, University of Florence, Italy**

Bicuspid Aortic Valve: Role of Multiple Gene Variants in Influencing the Clinical Phenotype.Sticchi E, De Cario R, Magi A, Giglio S, Provenzano A, Nistri S, **Pepe G, Giusti B.**Biomed Res Int. 2018 Sep 5;2018:8386123. doi: 10.1155/2018/8386123. eCollection 2018.PMID: 30255099

Role of TGFBR1 and TGFBR2 genetic variants in Marfan syndrome.De Cario R, Sticchi E, Lucarini L, Attanasio M, Nistri S, Marcucci R, **Pepe G, Giusti B.**J Vasc Surg. 2018 Jul;68(1):225-233.e5. doi: 10.1016/j.jvs.2017.04.071. Epub 2017 Aug 26.PMID: 28847661

8) **Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco, Milan, Italy**

Precise Therapy for Thoracic Aortic Aneurysm in Marfan Syndrome: A Puzzle Nearing Its Solution. Rurali E, Perrucci GL, Pilato CA, **Pini A, Gaetano R**, Nigro P, Pompilio G.Prog Cardiovasc Dis. 2018 Sep - Oct;61(3-4):328-335. doi: 10.1016/j.pcad.2018.07.020. Epub 2018 Jul 21. Review.PMID: 30041021

The face in marfan syndrome: A 3D quantitative approach for a better definition of dysmorphic features. Dolci C, Pucciarelli V, Gibelli DM, Codari M, Marelli S, Trifirò G, **Pini A**, Sforza C. Clin Anat. 2018 Apr;31(3):380-386. doi: 10.1002/ca.23034. Epub 2017 Dec 23.PMID: 29226593

Aortic dilatation in Marfan syndrome: role of arterial stiffness and fibrillin-1 variants. Salvi P, Grillo A, **Marelli S,** Gao L, Salvi L, Viecca M, Di Blasio AM, Carretta R, **Pini A**, Parati G.J Hypertens. 2018 Jan;36(1):77-84. doi: 10.1097/HJH.0000000000001512. PMID: 29210860

9) **Academic Medical Center, The Netherlands**

Surgical treatment of Marfan syndrome and related disorders is all about dealing with uncertainties. **Groenink M**, Koolbergen DR.Heart. 2018 Mar;104(6):454-455. doi: 10.1136/heartjnl-2017-312081. Epub 2017 Aug 16. No abstract available.PMID: 28814491

10) **Radboud university medical center, Nijmegen, The Netherlands**

No additional individual HTAD-related publications in 2018 (see collaborative publications, above).

11) **Erasmus Medical Center, Rotterdam, The Netherlands**

Aortic Dimensions and Clinical Outcome in Patients With SMAD3 Mutations.
van den Hoven AT, Bons LR, Baart SJ, Moelker A, **van de Laar IMBH**, van den Bosch AE, Bekkers JA, Verhagen HJM, van der Linde D, **Roos-Hesselink JW**. Circ Genom Precis Med. 2018 Nov;11(11):e002329. doi: 10.1161/CIRCGEN.118.002329. No abstract available. PMID:30571188

Automated 3D segmentation and diameter measurement of the thoracic aorta on non-contrast enhanced CT. Sedghi Gamechi Z, Bons LR, Giordano M, Bos D, Budde RPJ, Kofoed KF, Pedersen JH, **Roos-Hesselink JW**, de Bruijne M.Eur Radiol. 2019 Jan 23. doi: 10.1007/s00330-018-5931-z. [Epub ahead of print]PMID: 30673817

Screening for thoracic aortic pathology: Clinical practice in a single tertiary center. Bons LR, Uchoa de Assis L, Dekker S, Kauling RM, Cuypers JAAE, Verhagen HJM, Budde RPJ, **Roos-Hesselink JW**.

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Congenit Heart Dis. 2018 Nov;13(6):988-996. doi: 10.1111/chd.12663. Epub 2018 Sep 27.PMID: 30259670

12) **Karolinska University Hospital, Sweden**

No additional HTAD-related publications in 2018

13) **Guy's Hospital, London, UK**

No additional HTAD-related publications in 2018 (see collaborative publications, above).

Medium-Sized Arteries Working Group (MSA-WG):

Clinical Trials:

The French ARCADE (Angiotensin II Receptor Blockade in Vascular Ehlers Danlos Syndrome) trial is a double blind, randomized, placebo controlled, and multicenter trial that has the possibility of being extended to other HCPs in the MSA-WG to make it a multinational trial.

The aim of this study is to see if angiotensin II receptor blockade by irbesartan, administered alone or in addition to celiprolol (vEDS reference therapy), reduces the rate of onset of asymptomatic and symptomatic cardiovascular events over 24 months compared to placebo.

French study recruitment finished in 2018 and is currently ongoing. The MSA-WG group has been discussing the feasibility of extending the trial to other VASCERN HCPs. For the moment, the case report form (CRF) is being shared so that we the MSA-WG can standardize data collection for future analysis.

A Dutch/Belgium placebo-controlled clinical trial with irbesartan led by Bart Loeys, is still in application process. Once the protocol is ready there will be country specific applications from other MSA-WG HCPs and then data can be shared for joint research.

Research projects ongoing within the RDWG (with several HCP members):

The RaDiCo SEDvasc (REDCap) registry is a cohort of patients with vascular Ehler's Danlos Syndrome which is currently underway in 16 centers in France. The MSA-WG wishes to extend this cohort to include patients from the other HCPs of the MSA-WG, thereby increasing the number of patients in the cohort. The Rare Disease Cohorts Programme « RaDiCo » is coordinated by « Inserm », the French Institut of Health and Medical Research. Currently involving the HEGP Hôpital Européen Georges Pompidou, it will soon have other HCP centers from the MSA-WG participating as the various study documents have been translated.

Research projects ongoing within the RDWG (individual HCPs):

There are various research projects currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed.

Publications:

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The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (March 2018 –February 2019):

Frequency of de novo variants and parental mosaicism in vascular Ehlers-Danlos syndrome.Legrand A, Devriese M, **Dupuis-Girod S**, Simian C, Venisse A, Mazzella JM, Auribault K, **Adham S**, Frank M, Albuisson J, **Jeunemaitre X**. Genet Med. 2018 Nov 26. doi: 10.1038/s41436-018-0356-2. [Epub ahead of print] PMID: 30474650

HCP individual publications (March 2018 –February 2019):

1) **Guy's Hospital, London UK**

No additional MSA-related publications in 2018

2) **HEGP Hôpital Européen Georges Pompidou, Paris, France**

Natural history of gastrointestinal manifestations in vascular Ehlers-Danlos syndrome: A 17-year retrospective review. **Frank M, Adham S**, Zinzindohoué F, **Jeunemaitre X**. J Gastroenterol Hepatol. 2018 Oct 24. doi: 10.1111/jgh.14522. [Epub ahead of print] PMID: 30357907

Arterial Stiffening with Ultrafast Ultrasound Imaging Gives New Insight into Arterial Phenotype of Vascular Ehlers-Danlos Mouse Models. Goudot G, Papadacci C, Dizier B, Baudrie V, Ferreira I, Boisson-Vidal C, Tanter M, **Jeunemaître X**, Pernot M, Messas E, Mirault T. Ultraschall Med. 2018 Sep 21. doi: 10.1055/a-0599-0841. [Epub ahead of print] PMID: 30241104

Pathophysiology of carotid-cavernous fistulas in vascular Ehlers-Danlos syndrome: a retrospective cohort and comprehensive review. **Adham S**, Trystram D, Albuisson J, Domigo V, Legrand A, **Jeunemaitre X**, **Frank M**. Orphanet J Rare Dis. 2018 Jun 25;13(1):100. doi: 10.1186/s13023-018-0842-2. PMID: 2994099

3) **Ghent University Hospital, Belgium**

See this HCP's publications in HTAD-WG

4) **University Hospital of Antwerp, Belgium**

See this HCP's publications in HTAD-WG

5) **IRCCS Foundation Policlino San Matteo, Italy**

See this HCP's publications in HTAD-WG

6) **Azienda Socio Sanitaria Territoriale Fatebenefratelli – Sacco, Itlay**

See this HCP's publications in HTAD-WG

7) **Erasmus Medical Center, The Netherlands**

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See this HCP's publications in HTAD-WG

Pediatric and Primary Lymphedema Working Group (PPL-WG):

Clinical trials:

There are currently no collaborative clinical trials underway in the PPL-WG.
Research projects ongoing within the RDWGs (with several HCP members):

There is a collaborative PPL-WG research project currently underway on the genetics of primary lymphoedema. This research study is based at St George's University Hospitals and Derby Teaching Hospitals NHSF Trust is also a recruiting center involved. Together data will be used for phenotyping and genetic testing.
These two centers are equally participating in the 100,000 Genomes Project, an ambitious genomics project hoping to sequence 100,000 genomes from around 70,000 patients with rare disease (and their families) and cancer. St George's University Hospitals and Derby Teaching Hospitals NHSF Trust are contributing data to the lymphoedema group.

Research projects ongoing within the RDWG (individual HCPs):

There are various research projects currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed.

Publications

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative Publications (2018):

No collaborative publications for this group.

HCP individual publications (March 2018-February 2019):

1) **NijSmellinghe hospital, Drachten, The Netherlands**

No additional PPL-related publications in 2018

2) **St George's University Hospitals, London**

A Novel Splice-Site Mutation in VEGFC Is Associated with Congenital Primary Lymphoedema of Gordon. Nadarajah N, Schulte D, McConnell V, Martin-Almedina S, Karapouliou C, Mortimer PS, Jeffery S, Schulte-Merker S, Gordon K, Mansour S, Ostergaard P.Int J Mol Sci. 2018 Aug 1;19(8). pii: E2259. doi: 10.3390/ijms19082259.PMID: 30071673

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Human phenotypes caused by PIEZO1 mutations: one gene, two overlapping phenotypes? Martin-Almedina S, Mansour S, Ostergaard P. J Physiol. 2018 Mar 15;596(6):985-992. doi: 10.1113/JP275718. Epub 2018 Jan 31. PMID: 29331020

3) **AZ Sint-Maarten, Belgium**

Lymphatic supermicrosurgery for the treatment of recurrent lymphocele and severe lymphorrhea. Giacalone G, Yamamoto T, Hayashi A, Belva F, Gysen M, Hayashi N, Yamamoto N, Koshima I. Microsurgery. 2019 Feb 14. doi: 10.1002/micr.30435. [Epub ahead of print] PMID: 30767257

Ultra High-frequency Ultrasonographic Imaging with 70 MHz Scanner for Visualization of the Lymphatic Vessels Hayashi, Akitatsu, MD*; Giacalone, Guido, MD, PhD†; Yamamoto, Takumi, MD, PhD‡; **Belva, Florence**, MD, PhD†; Visconti, Giuseppe, MD, PhD§; Hayashi, Nobuko, MD¶; Handa, Mayumi, MT‖; Yoshimatsu, Hidehiko, MD**; Salgarello, Marzia, MD§ Plastic and Reconstructive Surgery – Global Open: January 2019 - Volume 7 - Issue 1 - p e2086

Splice-site mutations in VEGFC cause loss of function and Nonne-Milroy-like primary lymphedema. Fastré E, Lanteigne LE, Helaers R, **Giacalone G**, Revencu N, Dionyssiou D, Demiri E, Brouillard P, Vikkula M. Clin Genet. 2018 Jul;94(1):179-181. doi: 10.1111/cge.13204. Epub 2018 Mar 15. No abstract available. PMID: 29542815

Intraoperative imaging of lymphatic vessel using ultra high-frequency ultrasound. Hayashi A, Visconti G, Yamamoto T, **Giacalone G**, Hayashi N, Handa M, Yoshimatsu H, Salgarello M. J Plast Reconstr Aesthet Surg. 2018 May;71(5):778-780. doi: 10.1016/j.bjps.2018.01.013. Epub 2018 Feb 15. No abstract available. PMID: 29398613

4) **University Hospitals Leuven, Belgium**

The discovery of the lymphatic system in the seventeenth century. Part V: an ode to the nerves. Suy R, **Thomis S,** Fourneau I. Acta Chir Belg. 2019 Jan 21:1-7. doi: 10.1080/00015458.2018.1561797. [Epub ahead of print] PMID: 30663504

Reliability, Validity, and Feasibility of Water Displacement Method, Figure-of-Eight Method, and Circumference Measurements in Determination of Ankle and Foot Edema. **Devoogdt N**, Cavaggion C, Van der Gucht E, Dams L, De Groef A, Meeus M, Van Hemelrijck R, Heynen A, **Thomis S**, Orhan C. Lymphat Res Biol. 2019 Jan 16. doi: 10.1089/lrb.2018.0045. [Epub ahead of print] PMID: 30648912

Manual lymph drainage may not have a preventive effect on the development of breast cancer-related lymphoedema in the long term: a randomised trial. **Devoogdt N**, Geraerts I, Van Kampen M, De Vrieze T, Vos L, Neven P, Vergote I, Christiaens MR, **Thomis S**, De Groef A. J Physiother. 2018 Oct;64(4):245-254. doi: 10.1016/j.jphys.2018.08.007. Epub 2018 Sep 18. PMID: 30241913

An Epidemiological Survey of Venous Disease Among General Practitioner Attendees in Different Geographical Regions on the Globe: The Final Results of the Vein Consult Program. Vuylsteke ME, Colman R, **Thomis S**, Guillaume G, Van Quickenborne D, Staelens I. Angiology. 2018 Oct;69(9):779-785. doi: 10.1177/0003319718759834. Epub 2018 Feb 26. PMID: 29482348

5) **Helsinki University Hospital, Finland**

No additional PPL publications in 2018

6) **Primary Lymphedema Expert Unit of CRMR Rare Vascular Diseases (HEGP Hôpital Européen Georges Pompidou), France**

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Low-stretch bandages to treat primary lower limb lymphoedema: a cohort of 48 children. Benoughidane B, Simon L, Fourgeaud C, **Vignes S**. Br J Dermatol. 2018 Nov;179(5):1203-1204. doi: 10.1111/bjd.16884. Epub 2018 Sep 6. No abstract available.PMID: 29897619

[Lymphedema in patients treated with sirolimus: 15 cases]. Fourgeaud C, Simon L, Benoughidane B, **Vignes S**. Rev Med Interne. 2018 May 8. pii: S0248-8663(18)30529-0. doi: 10.1016/j.revmed.2018.04.018. [Epub ahead of print] French. PMID: 29752013

7) **University Medical Center Freiburg, Germany and Földi Clinic (special HCP partnership) European Centre for Lymphology, Merzhausen**

See this HCP's publications in VASCA-WG.

8) **Derby Teaching Hospitals NHSF Trust, U.K.**

Lymphedema Research Prioritization Partnership: A Collaborative Approach to Setting Research Priorities for Lymphedema Management.Underwood E, Woods M, **Riches K**, **Keeley V,** Wallace A, Freeman J. Lymphat Res Biol. 2018 Oct 24. doi: 10.1089/lrb.2018.0026. [Epub ahead of print] PMID: 30358472

The Prognosis in Palliative care Study II (PiPS2): study protocol for a multi-centre, prospective, observational, cohort study. Kalpakidou AK, Todd C, **Keeley V**, Griffiths J, Spencer K, Vickerstaff V, Omar RZ, Stone P. BMC Palliat Care. 2018 Aug 13;17(1):101. doi: 10.1186/s12904-018-0352-y. Erratum in: BMC Palliat Care. 2018 Nov 3;17(1):121. PMID: 30103711

Vascular Anomalies Working Group (VASCA-WG):

Clinical Trials:

The VASCA-WG currently has one clinical trial underway: The VASE (Vascular Anomaly-Sirolimus-Europe) is phase III multicentric study evaluating the efficacy and safety of sirolimus in Vascular Anomalies that are refractory to standard care. It is ongoing in Brussels (Cliniques Universitaires Saint-Luc), and Germany (University Medical Center Freiburg) and is completed in France (non VASCERN members: Caen, Amiens and Montpellier). A similar trial, testing the treatment of congenital vascular malformations using Sirolimus, is ongoing at the Radboud University Medical Center in the Netherlands.

Research projects ongoing within the RDWGs (with several HCP members):

-A research study on the genetic basis of **Generalized Lymphatic Anomaly/Gorham-Stout Disease (GLA/GSD)** with collaboration between two HCPs from the VASCA WG (**Cliniques Universitaires Saint-Luc (BE) and University Medical Center Freiburg (DE**) is ongoing.

-A research study of the genotype-phenotype in **Verrucous Venous Malformation/ Hyperkeratotic Cutaneous Capillary-Venous Malformation (VVM/HCCVM)** with collaboration between two HCPs from the VASCA-WG (**Cliniques Universitaires Saint-Luc (BE) and Our Lady's Children's Hospital Crumlin (IE) is ongoing.**

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Research projects ongoing within the RDWG (individual HCPs):

There are various research projects currently ongoing in individual HCPs, with currently no second ERN HCP participating. These will continue to be developed.

Publications:

The following list of publications is not exhaustive. We have tried to search for the most relevant publications to include in this report.

Collaborative publications (March 2018-February 2019):

No collaborative publications from the VASCA-WG between March 2018-February 2019.

HCP individual publications (March 2018-February 2019):

1) **Cliniques Universitaires Saint-Luc, Belgium**

Mutations in Chromatin Modifier and Ephrin Signaling Genes in Vein of Galen Malformation. Duran D, Zeng X, Jin SC, Choi J, Nelson-Williams C, Yatsula B, Gaillard J, Furey CG, Lu Q, Timberlake AT, Dong W, Sorscher MA, Loring E, Klein J, Allocco A, Hunt A, Conine S, Karimy JK, Youngblood MW, Zhang J, DiLuna ML, Matouk CC, Mane S, Tikhonova IR, Castaldi C, López-Giráldez F, Knight J, Haider S, Soban M, Alper SL, Komiyama M, Ducruet AF, Zabramski JM, Dardik A, Walcott BP, Stapleton CJ, Aagaard-Kienitz B, Rodesch G, Jackson E, Smith ER, Orbach DB, Berenstein A, Bilguvar K, **Vikkula M**, Gunel M, Lifton RP, Kahle KT.Neuron. 2019 Feb 6;101(3):429-443.e4. doi: 10.1016/j.neuron.2018.11.041. Epub 2018 Dec 18. PMID: 30578106

Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, Hoyoux C, Chopinet C, Clapuyt P, Hammer F, **Vikkula M, Boon LM**. Orphanet J Rare Dis. 2018 Oct 29;13(1):191. doi: 10.1186/s13023-018-0934-z. PMID: 30373605

Multiple Cutaneous and Mucosal Venous Malformations. **Boon LM, Vikkula** M. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2008 Sep 18 [updated 2018 May 17]. PMID: 20301733

2) **Radboud university medical center, The Netherlands**

Comprehensive molecular and clinicopathological analysis of vascular malformations: A study of 319 cases. Ten Broek RW, Eijkelenboom A, **van der Vleuten CJM**, Kamping EJ, Kets M, Verhoeven BH, Grünberg K, **Schultze Kool LJ**, Tops BBJ, Ligtenberg MJL, Flucke U. Genes Chromosomes Cancer. 2019 Jan 24. doi: 10.1002/gcc.22739. [Epub ahead of print] PMID: 30677207

Influence of infantile hemangioma severity and activity on QoL of patients and their parents: A cross-sectional study. Moyakine AV, Spillekom-van Koulil S, Küpers EM, van der Vleuten CJM. Pediatr Dermatol. 2018 Sep;35(5):628-634. doi: 10.1111/pde.13599. Epub 2018 Jul 17. PMID: 30015356

3) **Helsinki University Hospital, Finland**

No VASCA-related publications from 2018

4) **University Medical Center Freiburg, Germany**

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PIK3CA mutations are specifically localized to lymphatic endothelial cells of lymphatic malformations. Blesinger H, Kaulfuß S, Aung T, Schwoch S, Prantl L, **Rößler J,** Wilting J, Becker J. PLoS One. 2018 Jul 9;13(7):e0200343. doi: 10.1371/journal.pone.0200343. eCollection 2018. PMID: 29985963

5) **Our Lady's Children's Hospital Crumlin, Ireland**

Generalized lymphatic anomaly successfully treated with long-term, low-dose sirolimus. Dvorakova V, Rea D, O'Regan GM, Irvine AD. Pediatr Dermatol. 2018 Jul;35(4):533-534. doi: 10.1111/pde.13494. Epub 2018 Mar 26. PMID: 29582448

6) **Bambino Gesù Children's Hospital, I.R.C.C.S, Italy**

No VASCA-related publications from 2018

7) **Karolinska University Hospital, Sweden**

Long-term health-related quality of life in children with lymphatic malformations treated with sclerotherapy generally matched age-appropriate standardised population norms. Ghaffarpour N, Claesson G, Wester T, Boman KK. Acta Paediatr. 2018 Dec 17. doi: 10.1111/apa.14700. [Epub ahead of print] PMID: 30556934

Surgical excision is the treatment of choice for cervical lymphatic malformations with mediastinal expansion. Ghaffarpour N, Burgos CM, Wester T. J Pediatr Surg. 2018 Sep;53(9):1820-1824. doi: 10.1016/j.jpedsurg.2017.10.048. Epub 2017 Oct 16. PMID: 29173777

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