Dercum's Disease: Estimating the prevalence of a rare painful loose connective tissue disease

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Research

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Abstract

Background

In the United States (US), the Orphan Drug Act of 1983 defines a rare disease as affecting less than 200,000 individuals. In Europe, a rare disease or disorder is defined as affecting 5 individuals in 10,000 which the European commission reports to be approximately 246,000 individuals. Dercum's disease, also known as Adiposis Dolorosa, is a rare loose connective (fat) tissue disease that is characterized by painful lipomas (fatty masses). Orphanet, the National Organization for Rare Disease (NORD) and the United States National Institutes of Health (NIH) have classified Dercum's disease as a rare disorder. The prevalence of Dercum's disease is not well studied or understood. The objective of this paper is to estimate the prevalence of Dercum's disease, whether it is in fact a rare disease, and increase awareness for this painful disease.

Results

An in-depth literature review was conducted in PubMed, the UK Biobank, the U.S. Agency for Health Research and Quality Healthcare Cost and Utilization, by incidence of disease in medical practice, in social media forums and by internet search in order to understand, estimate and determine the prevalence of Dercum's disease. The prevalence of Dercum's disease was found to range from 150 to 150,000 in the US population.

Conclusion

The data collected in this paper meet the requirements of the Orphan Drug Act which requires 200,000 individuals or less to be affected by a disorder for it to be classified as rare. These conclusions may apply to Europe as supporting data was utilized from both Sweden and the UK. Further research must be conducted to better understand subclassifications of this rare disorder.

Background

Dercum's Disease also known as Adiposis Dolorosa or Morbus Dercum is a rare loose connective (fat) tissue disorder that is characterized by painful lipomas (fatty masses) or angiolipomas. Pain in fat tissue is one of the key characteristics of Dercum's disease. Despite pain in tissues such as muscle, bone or tendon being accepted by healthcare providers as a valid complaint, pain in fat tissue is less accepted or understood. Dercum's disease can be confused with other loose connective tissue diseases such as lipedema, a painful but common disorder affecting the limbs of women, or Madelung's disease, a painful disorder usually affecting upper body fat.(1) Dercum's disease is also commonly misdiagnosed as obesity(2) or fibromyalgia.(3) Painful lipomas in Dercum's disease can occur in any portion of the body; the most common locations affected are legs, chest, abdomen, pelvis, lower back, arms and buttocks; the

painful fat occurs less commonly on the head, hands and feet. Painful lipomas in fat vary in size from pea-sized nodules to the size of a fist or larger; smaller lipomas may be difficult to palpate and therefore the fat tissue, rather than lipomas, may be considered painful. Another unique feature of Dercum's disease is the lipomas are reported to have the ability to "appear overnight or morph in shape in real time".(4) An individual can develop Dercum's disease at any time in life, but it is reported to appear on average more often in women in the third decade of life.(5)

There are different types of Dercum's disease including obesity-associated, lipedema-associated, FML-type, found in 20% of individuals in families with familial multiple lipomatosis (FML),(6) Angiolipoma-Type, localized trauma-induced lipomas, infectious type and healing disorder type.(1) One paper noted infections such as Lyme's disease, histoplasmosis and coccidioidomycosis may precede the development of Dercum's disease.(7) Older descriptions of Dercum's disease refer to the size or locations of the nodules without any further insight into the disease such as family history, past history or whether angiolipomas are present or not.

The signs and symptoms of Dercum's disease include "chronic pain, fatigue, brain fog, insomnia, cardiac arrhythmia most often tachycardia (palpitations), gastrointestinal distress often similar to irritable bowel syndrome, muscle weakness, tremor or jerking of muscles (myoclonus), joint pains, insulin resistance and diabetes, hypothyroidism, and other autoimmune disorders".(2) The pathophysiology of Dercum's disease is unknown. The diagnostic criteria for Dercum's disease recommended by Hansson requires obesity and chronic pain greater than three months in fat tissue, although in one study, about 25% of people with Dercum's disease were not obese.(5) Additional criteria state that upon examination, the fatty lipomas in the fat tissue must be palpable.(2) Orphanet, NORD and the NIH(8) recognize Dercum's disease to be a rare disorder.

Methods

Multiple methods were used to formulate an estimation for the prevalence of Dercum's disease including: 1) an in-depth literature review conducted on PubMed using the search words: Dercum's disease, adiposis dolorosa and angiolipoma, 2) search for individuals with the diagnosis of Dercum's disease in the UK Biobank, 3) use of the U.S. Department for Health Research and Quality Healthcare Cost and Utilization (AHRQ's HCUP), assessment of incidence of disease in medical practice, 4) use of social media forums, 5) questionnaires to physicians who know Dercum's disease and 5) estimates from individual physician practices.

Results

1. **FML-Type Dercum's disease**: People with FML have multiple lipomas that are non-painful. In some families with FML, one or more people can develop painful lipomas consistent with Dercum's disease.(6) The prevalence of FML is reported as 1/50,000.(9) Using the estimate of 1/50,000 people having FML in the US, and 327M people in the US (2018 estimate), then 6,540 people potentially

have FML in the United States. In families of people with FML, about 20% will develop pain and signs and symptoms of Dercum's disease.(5) Twenty percent of 6,540 people with FML is 1,308 people in the US potentially with FML-Type Dercum disease (Table 1).

Table 1

Source, methods and outcomes for estimating prevalence of Dercum Disease

Dercum Disease (DD) Type or Resource	Methods	Prevalence Estimate
Familial Multiple Lipomatosis (FML)-Type Dercum's Disease	1/50,000 people in the US predicted to have FML(9) x 2018 estimated US population of 327 M people = 6,540 people in the US potentially with FML x ~ 20% will develop DD(5)	1,208
FML- and Angiolipoma-Type Dercum's disease	61 of 428 subjects from a 743,000-population study had multiple lipomas (lipomas and angiolipomas) = 1/12,000 × 2018 estimated US population of 327 M	27,250
United Kingdom (UK) Biobank- ICD-10 Code E88.2 Dercum's disease	• ICD-10 code E88.2 is assigned for DD and other lipomatous disorders • Of 410,293 people in the UK Biobank with ICD codes, 50 people had E88.2 code assigned • Assume all fifty people with E88.2 code had DD • Prevalence rate = 0.012% in this population x 2018 estimated US population 327 M	39,849
AHRQ HCUP database ICD-9 diagnosis of Lipoid Metabolic Disorder (NEC) 272.8	• AHRQ HCUP database search 2007–2014 for ED visits coded for ICD-9 272.8 • In 2014, 207 ± 32 (SE) visits by patients with 272.8 coding • Assume all patients had DD • Estimated rate for ED visits for ICD-9 code 272.8 = 1 per 1,000,000 (137,807,901 total visits; US population 318.6M) • Assuming for every 1 patient with DD with significant pain to visit the ED, 100 did not, 207 × 100 = 20,700	20,700
Social media forum participation rates extrapolated form MCAS to DD	• Estimated 50,000 diagnosed MCAS patients in the US and 24%-48% forum participation • Four DD forums online, with estimated participation numbers of 2,408 assuming no redundancy • Assuming 24% participation (from above), 100% participation = 10,033; if 50% participation; the prevalence of DD is 4,816	4,816
Prevalence of Dercum's Disease Survey of Physicians; Fat Disorder Research Societies Annual Congress	• Survey of physicians attending the Fat Disorder Resource Society Annual Congress 2017, 2018, 2019 • Average number of patients with DD per physician = 4 • ~ 1/1000 patients with DD are referred to physicians who specialize in fat disorders • Prevalence = 4 × 10 physicians x 1,000	40,000
Social Media Fat Disorder Patient Forums	• Data from fat disorder patient forums enriched for patients with DD, typically 2-3K patients on forums • 44 patients report having DD • Assume patient overlap in the forums • Social media group participation at a low rate = 1/10 – 1/100 = 44 × 10 and 44 × 100	440–4,440

Dercum Disease (DD) Type or Resource	Methods	Prevalence Estimate
Prevalence of Dercum Disease-Estimate Based on Internet Google Search	a) Google US monthly search volume for acute myeloid leukemia (AML; 27,100), leukemia (all types; 368,000) and DD (5,400); Search volume for DD = 1.46% of all leukemia searches and 19.9% of AML searches; According to the National Cancer Institute, ~ 414,733 people in the US living with all leukemia in 2016 × 1.46% = 6,055 b) AML US prevalence (132,727) x 19.9% = 26,412	a) 6,055 b) 26,412
Author (KLH)	• 2,500 patients/year with fat disorders • 6 patients with FML-type DD + 10 patients with angiolipomas = 0.64% prevalence x 2018 US estimated population of 327 M	115,000
Mast Cell Specialist	• 3000 + cases with mast cell disease; 10 patients had DD = 0.3%; Specialist estimates 50 M mast cell cases in the US population	150–150,00
Specialist in chronic fatigue syndrome and other complex chronic disease	• Of 1500 patients, 2 had DD = 0.1% • Assume 133M people in US with chronic illness(20)	133,000
Author (BRM)	4 cases of Dercum disease in 3000 patients over 10 years	0.13% patients
Author (TW)	• > 24 years in practice; ~30/20,000 patients with DD • If 10–100 physicians have 10–50 times as many patients with DD as KOL-3, the largest estimate of prevalence of people with DD based on those who seek treatment = 20 × 50 × 100	150,000
Abbreviations: AML – acute myelogenous leukemia; DD – Dercum's disease; ED – Emergency Department; ICD – International Classification of Disease; MCAS – mast cell activation syndrome; SE – standard error		

2. **FML-Type and Angiolipoma-Type Dercum's disease**: A population-based study of 743,000 inhabitants in Sweden(10) evaluated non-visceral lipomas histopathologically from 428 patients during a one-year period and retrospectively analyzed patient age, duration of symptoms, lipoma size, site (location and depth) and multiplicity of lipomas. Sixty-one people were found to have multiple lipomas (both simple lipomas and angiolipomas), and if we assume all had Dercum's disease, this represents a prevalence of 1/12,000 (61/743,000). While this subpopulation was not defined in the article as having Dercum's disease, it is likely that they may be patients with Dercum's disease since having multiple lipomas is a significant hallmark of Dercum's disease. Although Sweden and the US are different countries, a gross assumption towards the US population can be made. Using 1/12,000 prevalence and a US population of 327M (US estimate in 2018) would result in an estimated US prevalence of 27,250 patients with Dercum's disease.

3. **United Kingdom (UK) Biobank Estimate**: The UK Biobank is an international health resource and registered charity with the aim of improving the prevention, diagnosis and treatment of a wide range disorders (UK Biobank, n.d.).(11) In 2006–2010, 500,000 people aged between 40–69 years were recruited from across the United Kingdom to take part in this project. They underwent several measures, provided blood, urine and saliva samples for future analyses and detailed information about themselves, and agreed to have their health followed. International Classification of Disease (ICD)-10 codes are available for 410,293 participants. The ICD-10 code for Dercum's disease is E88.2, for Lipomatosis, Not Elsewhere Classified (NEC). This code includes other rare lipomatous disorders as well. Fifty people in the UK Biobank had ICD-10 code E88.2. If we assume all fifty people under this code had Dercum's disease of 410,293 people sampled, the prevalence rate in this population is 0.012%, confirming Dercum disease is rare in the UK. If we use these data to make a gross assumption for the US population of 327M people (estimate for 2018), then 39,849 people in the US could have Dercum's disease.
4. **The H-CUP Database by AHRQ**:(12) The HCUP database is maintained by AHRQ. A search was conducted on data from 2007 to 2014 for all emergency department (ED) visits by ICD-9 diagnosis, Lipoid Metabolic Disorder (NEC) 272.8. AHRQ maintains a free version of this database with ICD-9 codes from 2006 to 2014. The data after 2014 must be purchased and only from 2016 onward, are ICD-10 codes used.

   In 2014, 207 +/- 32 (SE) ED visits by patients with Lipoid Disorder NEC (ICD-9 272.8) were recorded across the US. From this data, the fraction of patients with 272.8 who had Dercum's disease is not known, but if a patient with Dercum's disease visited the ED for pain, they would likely receive the ICD-9 diagnosis code 272.8.

   Assuming all patients visiting the ED who were classified as having painful Lipoid Disorders were patients with Dercum's disease, the rate of ED visits for this diagnosis in 2014 was 1 per 1,000,000 emergency visits (137,807,901 total visits; US population 318.6M). Assuming that for each patient with Dercum's disease who had pain sufficiently serious to visit the ED, there were 100 who did not, the total prevalence of Dercum's disease for 2014 would be 207*100 = 20,700 cases. This methodology contains errors that would grossly overestimate the prevalence of Dercum's disease because of the assumptions that: a) all ED visits falling under this diagnostic code were for patients with Dercum's disease and b) they represent 1% of the population of people with Dercum's disease for whom pain was a reason to visit the ED.

5. **Social Media Forum Participation rates extrapolated from Mast Cell Activation Syndrome (MCAS)**: In MCAS patient forums, a group enriched for patients with Dercum's disease, there are typically 6 k -12 k patients per site. With an estimated 50K diagnosed MCAS patients in the US, this represents a 24%-48% forum participation. An assumption can be made that there is a comparable percentage participation among patients with Dercum's disease, as many patients with Dercum's disease have MCAS especially those with angiolipomas, as mast cells are common in these lesions.(1) There are four Dercum's disease forums on the internet, with participation numbers of 379, 391, 211 and 1,427

totaling 2,408, assuming no redundancy for individuals participating in more than one site (thus systematically over-estimating the numbers); assuming 24% participation, then 100% participation would give 10,033 total patients with Dercum's disease; if 50% participation, then the prevalence of Dercum's disease would be 4,816. If assuming only 10% participation, then the prevalence of Dercum's disease would be 48,160 (Table 1).

6. **Prevalence of Dercum's Disease from Specialists whose practices focus on the diagnosis and treatment of subcutaneous fat disorders**: A survey was conducted of physicians who attended the Fat Disorder Resource Society (FDRS; fatdisorders.org) Annual Congress in 2017, 2018 and 2019 about the prevalence of patients with Dercum's Disease in their practice. These are physicians who have focused part of their practice on diagnosis and treatment of Madelung's Disease, Dercum's Disease and lipedema. The survey respondents represent University based medical referral practices as well as private practices across the US. The average number of patients per physician with Dercum's Disease was 4 individuals (authors KLH and BRM were not included or surveyed). While it is logical that individuals diagnosed with or suspected to have Dercum's Disease or a related subcutaneous fat disorder would either self-refer or be referred to physician who specializes in the diagnosis and treatment of Dercum's Disease, it is quite possible that only a fraction of such individuals are either self-referred or referred by their primary medical providers. If only a small percentage of individuals with Dercum's Disease, 1/100 or 1/1000, are referred, then one would predict the prevalence of Dercum's disease to be at an upper limit, 4 (patients per physician)*10 physicians*1,000 = 40,000.
7. **Social Media Forum Participation Rates Extrapolated from Fat Disorders**: In patient forums with a focus on subcutaneous fat disorders, a group significantly enriched for patients with Dercum's Disease, there are typically 2-3K patients (on two forums). Of these patients, there are 44 patients who report being diagnosed with Dercum's disease on the two forums. These individuals could be duplicated with the support forums and may also be on other support forums. Most rare diseases have social media support group participation in the 20–50% range. However, assuming participation at the very lowest rates of 1/100–1/1000, the total prevalence would be for a lower limit, 44*100 = 440, and for an upper limit, 44*1000 = 4,440.
8. **Estimate Based on Internet Searches for Dercum's Disease (Google AdWords Research)**:(13) In 2013, the Pew Research Center conducted an Internet and American Life Project. They found that 35% of US adults search for information on medical conditions they or someone they know might have.(14) A significant portion of Google search volume represents individuals, their family, or close friends searching for information on new symptoms or information on a new medical diagnosis. Physicians increasingly use internet search to help with diagnosis of diseases, especially with uncommon diseases.(16) Physicians use Google searches to access sites such as Medline, Medscape, Up-to-Date, MD Consult, Ovid and may others to aid in diagnosis of their patients.(15, 16)

   The Monthly Search Volume for a disease on Google in the US was as follows: Acute Myeloid Leukemia (AML)- 27,100 Searches; Leukemia- 368,00 Searches (All Types); Dercum's Disease- 5,400 Searches. The search volume for Dercum's Disease is 0.0146 or 1.46% of that of all Leukemia

searches. The search volume for Dercum's Disease is 0.199 or 19.9% of AML searches. According to the National Cancer Institute,(17) it is estimated there were 414,773 people living with all kinds of leukemia in the United States in 2016. Based on these data, the prevalence of all types of leukemia and the relative percentage of internet searches of 1.46%, the estimated prevalence of people with Dercum's Disease is 6,055 individuals in the US. About 21,450 new cases of AML are diagnosed each year. Most will be in adults, according to the American Cancer Society. AML makes up 32% of all leukemia cases with a prevalence of 132,727 individuals in the US population. Based on the diagnosis and the relative percentage of internet searches of the two diagnosis of Dercum's Disease to AML of 19.9%, then 26,412 individuals in the USA would have Dercum's disease.

Physician Practices

1. **Author (KLH)**: Approximately 2,500 people per year with fat disorders were seen (by KLH), mostly patients with lipedema, six patients with FML-type Dercum's disease and 10 pts with Angiolipoma-Type Dercum's disease, a prevalence of Dercum's disease of 0.64% in this population. The prevalence of lipedema in the US is thought to be 11% in women(12) though the range is 5–39%. A majority of people with Dercum's disease are women.(4, 13) Assuming a US population of 327M of which 50% are women, results in total US lipedema prevalence of about 18M. If we apply the FML-type and angiolipoma type Dercum's Disease prevalence of 0.64% in people with fat disorders, we obtain an estimated number of about 115,000 patients with Dercum's Disease in the US (0.64% of 18M fat disorder patients).
2. **MCAS Specialty Practice**: A physician specializing in MCAS – a condition associated with Dercum's disease – has a patient mix that is 'enriched' for a higher prevalence of Dercum's disease than in many other practices. This physician has a direct total case experience of 3,000 patients over 10 years and another few thousand indirect case experience recalls with only about 10 patients in total with Dercum's disease, an incidence of at most, about 0.3%. This physician estimates 50,000 diagnosed cases MCAS cases in the US, with a prevalence rate that may be up to 50M in the US population. An upper limit prevalence of Dercum's disease would be 0.3%*50M = 150,000 cases, and a lower limit of 0.3%*50K = 150 cases.
3. **Complex Disease specialty practice**: A physician specialist with expertise in chronic fatigue syndrome and other complex chronic diseases reports 2 cases of Dercum's disease in a case experience of 1500 patients over 5 years, an upper limit, as this practice is enriched with complex cases. If one assumes that there are 133M people in the US with a chronic illness (nationalhealthcouncil.org), 0.1%*133M = 133,000 people with Dercum's disease in the US.
4. **Author (BRM)**: In 27 + years of medical practice, three patients with Dercum's disease were actively managed. Two other suspected cases over the past 2 years have been seen, (co-managed by author KLH), therefore a total of 4 unique patients with Dercum's disease in 3000 patients over 10 years for a prevalence rate of 0.13%.
5. **Author (TFW) with Estimates of Prevalence Inference from Reported Incidence: Survey of Colleagues Who Specialize in Subcutaneous Fat Disorders**: Most of the practice is focused on treating

Subcutaneous Fat Disorders for the past decade. In the past decade about 30 patients with Dercum's disease have been seen in the fat disorder focused practice, most of them in the past few years. Practice referrals come from throughout the US for subcutaneous fat disorders such as lipedema, Dercum's Disease and Madelung's Disease. Currently there are 20 patients with Dercum's disease of all subtypes. Several of the patients are co-managed with Dr. Herbst. As a conservative estimate, there are at most ten physicians in the US who focus on the diagnosis and treatment subcutaneous fat disorders such as Madelung's Disease, Dercum's Disease and lipedema; the most liberal estimate would be 100 physicians. If 10 to 100 physicians have 10–50 times as many Dercum's disease patients as similarly focused medical practices, the largest estimate of prevalence of individuals with Dercum's Disease based on those who are seeking treatment from physicians who specialize in the treatment of subcutaneous fat disorders would be 20*50*100 = 150,000 individuals with Dercum's disease.

Discussion

Dercum's disease is considered a rare disease by the National Institutes of Health, Orphanet and NORD, but there are few publications in support of this designation. The methods utilized in this paper favor the use of data gathered in the US but other methods utilized data from the UK and Sweden, as well as online forums and Google searches, therefore the estimates of prevalence in this paper can be considered useful for both the US and parts of Europe.

The requirement for data to support a determination of low prevalence or rarity presents a paradox. If the condition is rare, how will it be proven with data that is scarce to prove that it is rare? Rather, the proof, for now, must be made by inference. The methodology presented herein is such an approach. These methods provided a maximum (upper) limit of the estimate of the prevalence of this rare disorder, 150,000. According to Auvin, such an incidence-based approach to prevalence estimation should yield an estimate that should be adjusted downward.(18) Thus, care should be taken with current incidence-derived prevalence figures to not overstate the prevalence in rare diseases, as "methodological challenges in counting small populations, coupled with advances in rare disease discovery, may cause discrepancies".(18) According to Auvin, incidence-derived prevalence estimation should be reduced by 17%. This tells us that our estimations, however we compute them, are likely to be OVER-estimating the prevalence by 17%.

No matter the source or what method is applied, the maximum number for the prevalence of Dercum's Disease is estimated to be substantially less than 150,000 with the minimum Auvin correction of -17%, for an adjusted maximum upper limit prevalence estimate of 124,500. By other methods, the prevalence is much lower. One can, with assurance, reasonably assume that the rarity of Dercum's disease qualifies it to meet the important central criterion of orphan drug status (less than 200 k).

While there are different types of Dercum's disease, there is only one paper that estimates the prevalence of the Angiolipoma-Type Dercum's disease; there are no data to estimate the prevalence of other types.

Hansson et al.(19) described types as: I Generalized diffuse; II Generalized nodular; III Localized nodular; IV Juxta-articular while Herbst presented different types: Type I (possibly early Type II), juxta-articular (around the joint): Painful folds or nodular fat on the inside of the knees and/or on the hips; in rare cases only evident in the upper- arm fat; Type II, diffuse, generalized type: Widespread pain from fatty tissue found anywhere from head to the soles of the feet; Type III, nodular type: Intense pain in and around multiple “lipomas”, sometimes in the absence of obesity. If Type I is a precursor stage to Type II, then it could be considered one form. This makes it moot to consider these types separately. More recently, Herbst revised the Types referencing past history, family history and type of lipoma.(1) Subtyping may be significant for assessing the therapeutic index of a drug during a proposed Phase IIb study but is not helpful in assessing prevalence or its rarity. If the subtypes were different with respect to a pain measure, a subtype classification may have been helpful but does not help or hinder our estimate of prevalence.

Other considerations for DD disease definition relevant to clinical trials criteria

A questionnaire including 110 patients with Dercum’s disease disclosed common symptoms; these included pain, fatty deposits unaffected by weight loss, easy bruisability, sleep disturbances, impaired memory, depression, difficulty concentration, anxiety, rapid heartbeat, shortness of breath, diabetes, bloating, constipation, fatigue, weakness, joint aches and muscle aches.(5) It cannot be assumed that a patient with Dercum’s disease will have a given number or specifically any one of these associated symptoms. The association of these other symptoms suggest a systemic illness with local or focal manifestation in a painful fat compartment.

Conclusions

In summary, no matter the source or what method is applied, the maximum number for the prevalence of Dercum’s Disease is estimated by multiple practitioners to be substantially less than 150,000, even without the minimum Auvin correction of -17%. These data meet the requirements of the Orphan Drug Act which requires 200,000 individuals or less to be affected by a disorder for it to be classified as rare. These conclusions may apply to Europe as supporting data was utilized from Sweden, the UK, online forums and Google. Further research must be conducted to better understand subclassifications of this rare disorder.

Abbreviations

AHRQ HCUP - Agency for Health Research and Quality Healthcare Cost and Utilization

AML – acute myeloid leukemia

DD = Dercum’s disease

ED = emergency department

FML – familial multiple lipomatosis

ICD – International Classification of Disease

M - million

MCAS – mast cell activation syndrome

NEC – not elsewhere classified

NIH – National Institutes of Health

SE – standard error

UK – United Kingdom

US – United States

Declarations

Ethics approval and consent to participate

not applicable for this section

Consent for publication

not applicable for this section

Availability of data and materials

all data is referenced or listed; there is no additional repository of data or materials

Competing interests

the authors have no competing interests or conflicts of interest

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Authors' contributions

Natalie Munguia, Karen Herbst, Thomas Wright and B. Robert Mozayeni all contributed to writing and modifying the manuscript and all have accepted the final manuscript for publication

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