July 2014, Volume 1, Number 3

Social impact identified in and by the alpha-1 antitrypsin deficiency community

Sara Wienke[1,4], Charlie Strange[1,4], Deirdre Walker[1,4], Marvin Sineath[4], James Quill[4], Barbara Warner[4], Lucinda Shore[4], Susan Flavin[2,4], Pamela Williams[3,4]

[1]Division of Pulmonary and Critical Care Medicine, College of Medicine, Medical University of South Carolina, Charleston, SC, [2]College of Nursing, Medical University of South Carolina, Charleston, SC, [3]College of Nursing, University of Arkansas for Medical Sciences, Little Rock, AR, [4]Alpha-1 Community Research Partnership, Medical University of South Carolina, Charleston, SC

ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic cause for two common chronic conditions, emphysema and liver disease. The social impact of living with this rare genetic disease has been incompletely defined. The paper describes thematic analysis of qualitative data. The goal of this project was to identify the social burdens of this rare genetic disease that occur independent of symptoms.

Through two pilot studies, transcripts from focus groups and interviews with 42 patients and caregivers living with AATD were collected. Nvivo10 software was used to synthesize qualitative and thematic overarching domains.

Two domains with three respective subdomains each emerged: Rarity and Genetic Etiology. Combining these data with existing literature, a model was developed to explain the social impacts in this rare genetic disease. This model will inform the development of tools to measure and improve clinical practice and research for patients living with other rare inherited conditions.

Domains of social burden associated with a genetic diagnosis inform healthcare providers of areas where best practices in clinical care, support and future research require future development. In addition, domains support future development of psychometric instrumentation to measure the social burden of rare disease with a genetic etiology.

KEYWORDS

COPD, emphysema, genetic, antitrypsin, social burden, genetic determinism, alpha-1 antitrypsin deficiency

CORRESPONDING AUTHOR:

Charlie Strange, MD
Division of Pulmonary Medicine
Medical University of South Carolina
MSC 630
Charleston, SC 29425
e-mail: strangec@musc.edu
Tel. 843-792-3174
Fax: 843-792-0297

Submitted: 13 May 2014 / Accepted: 12 July 2014

Copyright © 2014 Charlie Strange *et al.*; Division of Pulmonary Medicine, Medical University of South Carolina. This is an open access article licensed under the Creative Commons license Attribution-Noncommercial 3.0 Unported, which permits to copy and redistribute the material in any medium or format and remix, transform, and build upon the material for non commercial use and provided that the original work is properly cited. To view a copy of this license, visit http://creativecommons.org/licenses/by-nc/3.0/

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n° 305690: RARE-Bestpractices project: www.rarebestpractices.eu. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

WWW.RAREBESTPRACTICES.EU

INTRODUCTION

Scientific, clinical and public interest drives research to identify genetic factors that increase risk for common, adult onset, chronic conditions. Dramatic technological advances such as improvements in genetic testing, sustain this interest. The interest is framed by increasing amounts of genomic information for clinicians and patients to consider, combined with these respective stakeholders' cognitive appraisal of the utility and impact of the information. The manner in which providers, patients and the public appraise genetic information impacts these stakeholders' social relationships.

In two pilot studies, a community living with social relationships impacted by genetic information (alpha-1 antitrypsin deficiency) shared their perceptions about how the genetic information and disease rarity influence their relationships with others. The research aim driving both of these studies was to define the domains of social burden experienced by individuals with alpha-1 antitrypsin deficiency. The purpose of this paper is to synthesize and describe the results and identify their implications for future research and clinical practices serving patients living with rare, inherited conditions that clinically present as common chronic conditions.

Alpha-1 antitrypsin deficiency (AATD, Alpha-1) is a rare genetic disorder caused by inherited deleterious polymorphisms in the *SERPINA1* gene. The PiZZ deficiency is one of the most common inherited metabolic disorder in Caucasians of northern European descent with an incidence of 25 in 100,000 births worldwide [1]. The most common genotypes associated with severe deficiency are caused by inheritance of 2 abnormal protease inhibitor S or Z allelles (PiSZ or PiZZ) which produce misfolded AAT protein in the liver that predisposes to cirrhosis. In addition, the low serum levels of this antiprotease predispose to emphysema and chronic obstructive pulmonary disease (COPD). Therefore, in persons with AATD, the common diseases cirrhosis and COPD have a genetic basis. In COPD, 1-3% of cases are caused by AATD. These estimated 70,000-100,000 United States individuals of which <10,000 are diagnosed form the community that began this study [2,3,4]. Internationally, >1,100,00 individuals have severe deficiency which led to an additional international focus.

Importantly, AATD produces a multifactorial disease state influenced also by environmental exposures. In the lung, exposure to fumes and smoke modify risk of developing COPD suggesting that a clean air environment and avoidance of cigarette smoking is important [5,6]. In the liver, maintaining a normal weight is recommended to avoid the co-morbidity of non-alcoholic hepatosteatosis (NASH) cirrhosis. The symptoms experienced with AATD lie within a spectrum of variability. At one end of the spectrum, individuals may live a long and healthy life without the need for any therapy. At the other end of the spectrum, severe lung or liver disease requires costly medications and/or organ transplantation despite maintenance of a clean air environment and normal weight. An infantile form of the disease, occurring in approximately 5% of ZZ patients, causes life threatening liver disease in childhood.[7] A skin disease, necrotizing panniculitis, is rarely seen. Multiple family generations are often affected with the genetic carrier state having a more mild risk for lung and liver disease.

Testing recommendations were established in 2003 by the American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. In short, testing has level A (highest level) expert opinion recommendations for symptomatic individuals with emphysema, COPD, or asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators, unexplained liver disease, necrotizing panniculitis, or siblings of a severely deficient individual. These recommendations have been incompletely actualized.

AATD is a multifactorial disease state because the development of symptoms stems from genetic, epigenetic, and environmental factors. This variability makes AATD a condition that has heterogeneous burdens. AATD rarity, the overlay of common clinical diseases of COPD and cirrhosis, and the genetic information itself all interact to affect social relationships. This paper and the studies synthesized focused on impact experienced by individuals with AATD independent of clinical symptoms. Qualitative data obtained through qualitative interviews and focus groups from two studies are synthesized for this paper. Participants were invited to describe social experiences with healthcare settings, healthcare professionals, family, friends, the public, insurance, employers, coworkers and fellow community members where the rarity or genetic information of their condition had impact. The range and level of social consequences related to the genetic basis and/or the rarity of illness has poorly defined dimensions; and consequently lacks psychometric development for measurement.

METHODS

Two pilot studies funded through pilot grants from the Alpha-1 Foundation and PCORI were conducted to obtain data for this paper. Both studies were conducted with a community based participatory research partnership (CBPR) approach and were approved by the Institutional Review Board at the Medical University of South Carolina. Participants were recruited through the Alpha-1 Research Registry at the Medical University of South Carolina. Interviews were conducted face to face or via telephone using probes to elicit patient responses. Focus groups were facilitated by face to face meetings at support group or patient conference venues. The trained partners conducting the interviews and focus groups included a genetic counselor (Alpha-1 Foundation sponsored), nurse scientist (principal investigator on both studies), and pulmonologist (recognized expert in treatment and clinical science of AATD). Support group leaders, patients, advocates and patient navigators represented the community partners of the CBPR team. CBPR approaches to research incorporate academic and community stakeholders to enhance the relevance and dissemination of the research results to the patient community. The Alpha-1 community is a well-connected group with a strong

collective identity facilitated by the efforts of the Alpha-1 Foundation [8]. For these studies, all partners were involved in some aspect of study design, data collection, recruitment, data analysis and/or writing this report.

The qualitative data came from interviews and focus groups with individuals either having AATD or were family members/caregivers of those with AATD. Both studies had similar aims to describe the social impact of living with AATD as a multidimensional set of constructs not yet captured by current psychometric instruments. Focus groups and interviews were conducted in Oklahoma, Colorado, Texas, South Carolina, Florida, Ohio and in Barcelona. The Barcelona groups were comprised of individuals from Australia, Canada, Germany, New Zealand, Norway, Portugal, and Spain.

Focus groups ranged from 5-10 subjects included adult male and female patients, caregivers and family members attending patient education days. Ages ranged from 21 to 84 and all were Caucasian race. Those with genotypes included 10 MZ, 22 ZZ, 2 SZ, 1 SNull, and 1 MF. In total, transcripts from 42 participants were analyzed to identify themes. NVIVO 10 software supported coding transcripts into nodes or themes, auditing of each other's coding and audit trail preparation. Through a three stage systematic synthesis process detailed by Thomas and Harden,[9] four members of the CBPR team synthesized the results within the respective studies, and organized nodes identified into tables using inductive reasoning. Reported impacts, unrelated to symptoms, fell into the two overarching thematic domains: those related to the rarity of AATD and the other related to the genetic basis of disease in AATD. Once our analysis reached saturation or point at which no new nodes were identified, the study team discontinued data collection procedures.

Data analysis supported the team's development of a rich synthesis of patient centered thematic topics that will be used to generate items for future scale measurement. We also reviewed literature for thematic domains that explain social impact of rare conditons.

Operational definitions for coding frameworks

Several operational definitions were developed by the data analysis team in the original coding and were used for the synthesis of the three studies. Social burden was defined as those hardships, challenges, frustrations and duties related to interactions within social settings such as healthcare, social, educational, public service, and employment systems. Social impact became a broader term to operationalize, including burden and the positive outcomes resulting from an AATD diagnosis. In both studies, the aims were framed to illuminate social burdens as a result of having a genetic basis for a disease as separate phenomena from burden related to the symptoms of the condition itself.

RESULTS

Two large impact domains were identified and are summarized in *Table 1*: Rarity and Genetic Etiology. Each impact domain was associated with a specific burden sub domains associated with specific patient burdens. For Rarity, the sub-domains identified were 1) Lack of provider knowledge associated with diangostic delay, provider mistrust and vindication once accurate diagnosis achieved, 2) Lack of public and family knowledge asociated with stigma and explanation fatigue and, 3) Access to information which was associated with misunderstandings about alpha-1 in the patient/family population. For Genetic Etiology, sub-domains identified were 1) Sharing genetic informaiton with family members which was associated with testing decisions, guilt, fear for future generations, and strain within the family dynamic, 2) Genetic determinism associated with fear for future health, susceptibility induced vigilance and potential behavior modification, and 3) Genetic discrimination associated with impact on faith in healthcare and payment (insurance) systems and impact on job status.

Lack of provider knowledge

Patients with AATD reported going many years being diagnosed with COPD without being tested to see if they have alpha-1 antitrypsin deficiency, despite recommendations that any individual with COPD be offered testing.[11] This results in a diagnostic delay averaging 6.3-7.2 years following initial onset of symptoms and sometimes requires the patient to see multiple doctors before finding the cause for their symptoms.[12,13] Discussions of this delay led to patient descriptions of mistrust in their doctors and feeling vindicated when they receive the correct diagnoses. Once diagnosed, patients often seek out providers who either specializes in the condition (Alpha 1 Foundation Clinical Resource Center), find a provider willing to educate themselves or look to other patients with AATD to learn treatment and management strategies.

"Well, when I first was diagnosed with cirrhosis, when I had the serious bleed back in 2010…the doctors kept saying, well the reason you've got cirrhosis is because you drank too much, you drank too much, you drank too much. And I kept trying to tell them, you know, 'no, I didn't drink that much.' You know, I was a social drinker…So, when I got to MUSC and they did all the testing and they said, you know, it wasn't from the alcohol, it was from the alpha-1, it was actually a relief to me because finally somebody saw what I'd been trying to tell them all along"- SC PCORI Interview

Lack of public knowledge

Knowledge is also lacking in friends, family and community members of the diagnosed individual. AATD patients described fatigue and frustration at the frequency in needing to explain to everyone the dynamics of the condition. Additionally, many reported feeling blamed or judged by others that their symptoms were brought on solely as the result of their behavior (i.e. smoking, drinking).

"Most people don't know about it. You know, they are rather surprised to find out that there is a genetic component"- SC

PCORI Interview

"…he's got cirrhosis of the liver, it's like people assume you've got a drinking problem."- SC PCORI Interview

"Oh, like 10 times a day. (laughter) Well, mostly, too, I-I-I volunteer sometimes because they think, I know they think I got this from smoking and that really irritates me"- OH PCORI focus group 2

Lack of access to knowledge

Study participants reported finding current and accurate information about their condition challenging. Patients and caregivers reported travelling a great distance to visit clinical resources centers sponsored by the Alpha-1 Foundation. Many reported travel to meet for education days or support group meetings sponsored by the Alpha 1 Foundation. Participants rarely described their local physician as their best source of information regarding successful strategies to manage their conditions.

"…it led me to look online, … I found a suport group and I called a lady at the support group, who turned out to be at MUSC in Charleston. And I told her all…and she said, would you mind, after I had about an hour discussion with her, she said, do you mind …That's how I learned, and so, and I am still learning."- SC PCORI Interview.

Table 1. Results of thematic synthesis: domains & subdomains framework

Impact Domain	Burden Sub-Domain	Domain's Abstracted Meaning/Definition	Psychosocial Sequelae to Patient
Rarity	Lack of provider knowledge- impacts provider/patient relationship	Provider lacks experience and knowledge on screening and/or treating the disease state.	Diagnostic delay
			Provider mistrust
			Patient perceives vindication with diagnosis
	Lack of knowledge Family Public Impacts patient/family and patient/public relationships	Includes family, friends, social acquaintances (e.g. dating); misconceptions and generalizations make individuals with the disease feel isolated or different	Perceived stigma
			Explanation fatigue
	Access to information (internet, library, informed provider)	Difficult to find accurate information with current online and print resources. Specialists are few and far between.	Misunderstandings about the disease state
Genetic Etiology	Sharing genetic information with family members Impacts patient/family relationship	Genetic information comes with responsibility to inform family members about risks and this information impacts the relationship	Testing decisions
			Guilt
			Fear for future generations
			Strain within family dynamic
	Genetic Determinism and/or Fatalism (moderator) Impacts potentially all relationships	Level to which participant believes that genes alone determine future health. Perceived control or lack thereof over the future.	Fear for future health
			Susceptibility induces behavioral modification & vigilance
			Fear for future family's generations
	Genetic Discrimination	Genetic diagnosis impacts the patients concerns for insurance coverage and payment as well as employment status.	Impact on faith in healthcare and payment systems
			Impact on job status

Sharing information with family/impact on family relationships

The described individuals' diagnosis of an inherited condition implied the entire family received a diagnosis. Guilt from older generations and fear for future generations were commonly described experiences.

"So the family, the extended family, they don't want to look at-they don't want to look at me in the eye," "…My dad trying to…when I was diagnosed, trying to kind of cope with it, he's talking to his brother, he talks about twice a week, and my dad said that he said to him, he said let's talk about something more pleasant. Let's talk about cows."- SC PCORI Focus Group

"Very negatively. Uh, she-she [mother] felt to blame because of how I was explaining it of course, that it was genetic and that it had been passed down from both her and my father."-OH PCORI Focus Group 1

"He [father] has apologized to me and saying that I'm sorry that you have this. Um, I don't get to see my brothers and sisters that much, even though we live in close proximity because we all have our own life. But, I think he might feel some, a little bit of guilt."- OH PCORI Focus Group 2

"We're working on it (sharing diagnosis with family), and I'm scared, because my son is 27 and he smokes. And I'm scared for him."-TX Foundation Focus Group 1

"We talked about the possibility of having children who were affected with alpha-1" (talking about his experience being a genetic carrier married to genetic carrier). "- MO PCORI Interview

Beliefs in genetic determinism and/or fatalism moderate fears for future health and behavior change

Many participants expressed fear or anxiety for their future health. Knowing about the genetic component of AATD evoked a range of responses. Some perceived a lack of control while others responded with heightened vigilance to exert control environmental factors. We termed the latter phenomenon as "susceptibility induced vigilance". Asymptomatic participants that already knew their genetic information described avoidance behaviors regarding environmental exposures harmful to their lung and liver. Those that were already symptomatic described avoiding environmental exposures that can exacerbate their disease or cause further lung and/or liver damage. Individuals believing there is nothing they can do appeared to fully submit to fatalistic beliefs. There was expression of relief that there was a genetic explanation for their illness that partially relieved them of self-blame for smoking causing their symptoms.

"You're a victim, I mean, you got it, you had no decision, your choices and your decisions in life had nothing to do with you getting it, so I think that comes into play psychologically when you find out that you do have it"- OK Foundation Focus Group

"I feel very blessed and very lucky because I found out early before I had symptoms and that's why I'm able to do the things I'm able to do now. Umm, because we immediately got on the ball and started taking care of, you know, we altered our life, the way that we need to, so today I don't have a lot of symptoms"-OK Foundation Focus Group

"When we got tested we found out, you now, who all had the, you know, the type and stuff. And I-I was a smoker. I quit smoking that minute."- OH 1, PCORI Focus Group

Genetic discrimination

Participants described how their genetic diagnosis impacts their job, social relationships and perceptions of discrimination based on their genetic information.

"Well, when I cough at work all the time I just say, 'well, you know, this is something you're gonna have to put up with' cause they'll say 'are you getting sick?' and I'll say 'no, I just found out this is probably something I'm going to have for the rest of my life and y'all are just going to have to put up with that gross sounding cough, sorry."-OK Foundation Focus Group

Positive Social consequences

While we chose to focus our analysis on the negative social consequences of a rare genetic disease for this work, we would be remiss to not share that persons with AATD reported positive social consequences as well. Some patients reported that new support resources became available to them as a result of networking with other persons with AATD after obtaining the correct diagnosis. Participants also described how the challenges in their social experiences gave their life new purpose and meaning. This may be the same as the redemptive adjustment defined by McAllister et al (2007).

"It gave me focus. It gave me, where I was trying to figure out something in my life to focus on and I was just kind of rambling around and all of the sudden when I was diagnosed it gave me complete focus. It gave me focus in a career. It gave me focus in everything. It gave me passion for something that I was lacking. So, I guess I am fortunate enough that I've not been, that it's affected me physically, but from a positive perspective it's given me focus full realm and um, I like doing my job. I like helping other alphas. I like educating."- SC Focus Group

Model Formation

Literature review found confirmation of our findings in the work of others in this field. The distilled themes in our synthesis suggest a relationship to the elements of the conceptual work by McAllister.[10] A proposed conceptual framework resulted from conceptual propositions of how to harmonize the McAllister model with our work. This newly proposed framework, seen in ***Figure 1***, reflects the implications of our synthesis and frames future study of the causal relationships and modeling of the related variables.

DISCUSSION

From the results drawn through the synthesis of our qualitative data, we conclude that persons living with AATD experience a variety of dimensions of social impact that interact and have the capacity to influence all of their social relationships. Rarity and genetic etiology of AATD has discrete consequences that affect the individuals' relationships with providers, the healthcare system, family, and public and social support systems. We found that patients with AATD are resilient in dealing with a genetic condition that results in heterogeneous clinical presentations. Our efforts to model the experience of living with AATD may be refined in future attempts to study the social impact of AATD as well as other similarly defined conditions. Specifically, we would like to clarify further the redemptive adjustment and what factors can enhance an individual's ability to reach that point and minimize some of the burdens identified.

We would hope that this model can be generalized to other genetic conditions. Validation cohorts in AATD and in other genetic diseases are required from US and international populations. Anticipated refinements would likely come from study of some pediatric conditions since the burden of caregivers was not incorporated into this model. However, *Figure 1* and *Table 1* specifically do not include mention of AATD and can be tested in other conditions.

Limitations

The study recruitment pool (patient registry) and those recruited were both convenience samples. As a result, the full range of individual perceived burdens or coping may not be represented. Qualitative analysis in each respective study reached a point of dimensional saturation within the convenience sampling methods. Additionally, data was not analyzed based on genotype or presence of clinical symptoms. It is possible that burdens differ based those factors, among others. Furthermore, we did not distinguish social burdens perceived by caregivers in reference to themselves. Caregivers typically discussed their views on burdens suffered by the diagnosed individual. To fully understand the social burdens of any genetic diagnosis, it is important to understand how it also impacts those nearest to its effects.

Implications for future research

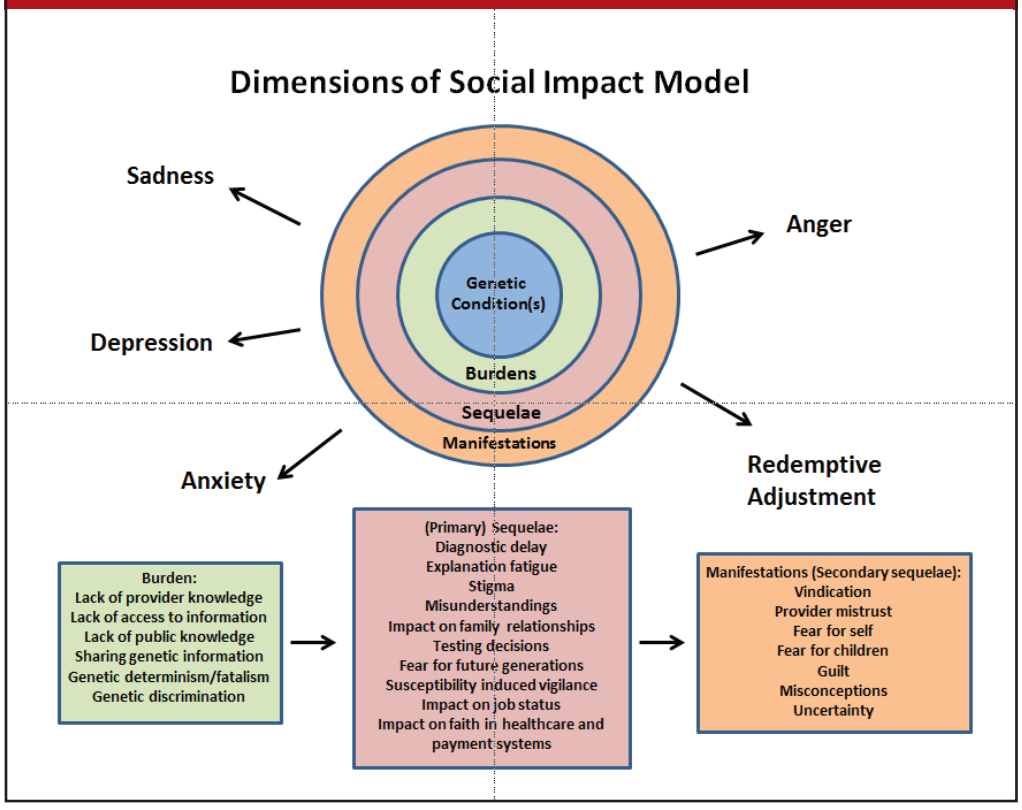
The results of this paper suggest refinements and expansion of an existing conceptual framework proposed by McAllister et al,[10] reflected in *Figure 1*. Future research is needed to understand and identify causal, modifying and mediating effects between negative and positive social consequences and emotional effects. For example, future research may clarify whether those who find new meaning or purpose of their life as a consequence of living with a rare genetic condition is a predicting variable for the emotional effect referred to as "redemptive adjustment" [10]

Discovery in associative or predictive relationships between these domains and those emotional outcomes described by McAllister et al,[10] can guide and inform intervention development in the future in order to promote positive patient centered outcomes. This exploration will require measurement of the domains of social impact identified thus far. Measurement development for the reported domains and subdomains is the future direction of our community based research partnership's program of research.

Implications to clinical practice

AATD may be most appropriately thought about as a multifactorial condition that includes genetic predisposition to common, chronic diseases. While inheritance is

Figure 1. Proposed ecology of social impact variables: associated burdens, sequelae & emotional manifestations in rare genetic condition(s)



certainly Mendelian, and blood levels of someone with a ZZ genotype will certainly be deficient, the development of symptoms is not guaranteed. However, most individuals that are diagnosed with COPD also have a history of environmental exposures. Additionally, there are likely epigenetic mechanisms that are not yet fully understood that modulate the risk for lung and liver disease.[7] As awareness of such conditions increases, counseling and patient education may evolve to be similar to other common, complex diseases. Furthermore, this is a condition where early testing and awareness may result in lifestyle changes that could mitigate onset and development of symptoms. For that reason, it is necessary to understand how this diagnosis impacts an entire family, in order to promote positive outcomes for individuals that are being tested as well as their family members.

Acknowledgments:
This research was supported by grants from the South Carolina Clinical and Translational Research Institute (UL1 RR029882), a Patient Centered Outcomes Research Institute (PCORI) pilot award, the Alpha-1 Association, and the Alpha-1 Foundation.

REFERENCES

1. Janciauskiene S, Ferrarotti I, Laenger F, Jonigk D, Luisetti,M. Clinical utility gene card for: α-1-antitrypsin deficiency. Eur J Hum Genet. 2011. Epub 2011 Jan 19.
2. Stoller JK and Aboussouan LS. A review of α_1-antitrypsin deficiency. Concise Clinical Review. Am J Respir Crit Care Med. 2012;185(3):246-59.
3. Sclar DA, Evans MA, Robison LM, Skaer TL. α_1-Proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to α_1-antitrypsin deficiency. Clin Drug Investig. 2012;32(5):353-60
4. Rahaghi FF, Sandhaus RA, Strange C, Hogarth DK, Eden E, Stocks J, Krowka MJ, Stoller JK. The prevalence of alpha-1 antitrypsin deficiency among patients found to have airflow obstruction. COPD 2012;9(4):352-8
5. Ioachimescu O. and Stoller JK. A review of alpha-1 antitrypsin deficiency. COPD 2005;2: 263-75.
6. Molloy K, Hersh C, Morris V, Carroll T, O'Connor C, Lasky-Su J, Green C, O'Neill S, Silverman E, and McElvaney, N. Clarification of the risk of chronic obstructive pulmonary disease in α_1-antitrypsin deficiency PiMZ heterozygotes. Am J Respir Crit Care Med. 2014; 189(4):419-27.
7. Teckman JH. Liver disease in alpha-1 antitrypsin deficiency: Current understanding and future therapy. COPD 2013;10 (S1):35-43.
8. Williams PH, Finn S, Strange C. (2013) Assessing Community Engagement Factors To Support Individuals Impacted By A Rare Disease: Alpha-1 Antitrypsin Deficiency. The Internet Journal of Advanced Nursing Practice. 2013; Volume 12 Number 1.
9. Thomas J. and Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:45
10. Mcallister M, Davis L, Payne K, Nicholls S, Donnai D, and McCleod R. The emotion effects of genetic diseases: Implications for clinical genetics. Am J Med Genet. 2007;143A: 2651-2661.
11. ATS/ERS Statement. American thoracic society/European respiratory society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168: 818-900.
12. Campos, M., Wanner, A., Zhang, G., and Sandhaus, R.A. Trends in the diagnosis of symptomatic patients with α_1-antitrypsin deficiency between 1968 and 2003. Chest 2005;(3):128:1179-86.
13. Stoller JK, Sandhaus RA, Turino G, Dickson R, Rodgers K, and Strange C. Delay of diagnosis of α_1-antitrypsin deficiency: A continuing problem. Chest. 2005;128(4):1989-94.