The “11 Factors” of Primary Aldosteronism

Prepared by the Primary Aldosteronism Foundation

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Disease Prevalence

The severity spectrum of primary aldosteronism (PA) spans a continuum, as illustrated by Brown et al. (2020) in an article named by the American Heart Association one of the biggest advances in heart disease and stroke research of the year:

- Over 20% of resistant hypertensives have severe forms of PA,
- Moderate forms of PA are found in over 35% of all other hypertensives, and
- Overt PA without hypertension can be seen in over 10% of individuals.

Extrapolation from the prevalence of resistant hypertension (Carey et al., 2019) using 2021 US census data indicates that 40 million Americans are affected by severe and moderate forms of PA.

Prevalence of PA's Severe Forms	US Population > 18 years old
45% have hypertension	116 million
11% of them have resistant hypertension	13 million
22% of them have PA	**2.86 million**
Prevalence of PA's Moderate Forms	**US Population > 18 years old**
45% have hypertension	116 million
89% of them have non-resistant hypertension	103 million
37% of them have PA	**38.1 million**

Problem Statement

Although discovered over 6 decades ago, PA remains mostly undiagnosed and untreated (Jaffe et al., 2020; Ruhle et al., 2019).

Number of Undiagnosed Patients	US Population > 18 years old
Less than 95% of those with severe forms of PA	**2.72 million**
Needed ARRs	2.72 million
Needed adrenalectomy	0.95 million
Needed MRAs/ASIs	1.77 million
Less than 95% of those with moderate forms of PA	**36.2 million**
Needed ARRs	36.2 million
Needed adrenalectomy	12.7 million
Needed MRAs/ASIs	23.5 million

Considering the gap between high prevalence and near absence of diagnosis and treatment, PA constitutes a major public health issue:

- In studies that have matched patients for hypertension control, patients with PA have 4- to 12-fold higher rates of myocardial infarction, stroke, coronary artery disease, and arrhythmias, and poorer health-related quality of life than people with primary hypertension.
- Diagnosis and treatment need to be provided to 12% of the American population.

The above gap is further illustrated by the paradox of scientific publications inversely proportional to disease prevalence. Parkinson's and HIV are respectively 60 and 1,000 times less prevalent than PA, yet 14 and 35 times more articles have been published on these two diseases respectively than on PA.

In this context, understanding aldosterone excess remains inevitably fragmented. Only a third of patients qualify for potentially curative adrenalectomy. Only two drugs, both with limited efficacy and tolerability, are available to the remaining majority, and one of them is not approved by the FDA for treatment of the disease.

Common Journey to Diagnosis and Lived Experiences

Nina

Residence: Illinois, USA
Diagnosis: bilateral disease
Time to diagnosis: over 10 years

Before Diagnosis

As a teenager, I suffered with symptoms of low potassium (not knowing at the time that primary aldosteronism (PA) was the cause) and associated very high uncontrolled blood pressure. My primary care physician (PCP) kept giving me potassium at checkups, telling me it's low but never following up or connecting it to anything.

When I was in grad school, I was diagnosed with anxiety at an ER visit for elevated heart rate, difficulty breathing, and stomach issues. I thought I was having a heart attack. My blood pressure was 165/110. I was given every blood pressure medicine you can name by my cardiologist, but my diastolic pressure wouldn't lower and I did not feel well on the prescribed drugs.

I visited the ER several more times with heart palpitations, extremely high blood pressure and even what felt like panic attacks that I had never experienced before. I had extensive testing from an endocrinologist. I was tested for Cushing's and every other disease suggested to me by family and by physicians trying to find an answer. I couldn't sleep. My body thought bedtime was "get up time." I urinated several times in the night, resulting in no sleep at all for me. I would get headaches and go through days of debilitating fatigue. I also discovered that I had early onset cataracts.

Diagnosis

In 2017, about ten years after the onset of my first symptoms, I was researching on my own one day, as I often did, and realized I might have PA. I asked to be tested for it and was told: "we are looking for the horse, not the zebra" and "it is highly unlikely you have this." The doctor ordered a CT scan, which showed an enlarged left adrenal gland (hyperplasia). He also ordered 24-hour urine testing, aldosterone and renin testing, and other bloodwork. This was followed by two rounds of adrenal venous sampling (the first one was unsuccessful accessing the right adrenal gland), after which I was formally diagnosed with PA. I'm not a surgical candidate and I'm going to be on medications forever.

Treatment

To better manage my care, I decided to find the best doctor reasonably near me, a well- known physician and professor at a university in Chicago.

After diagnosis, I started on spironolactone. The dosage of spironolactone was later increased as bloodwork was tested periodically.

Since Treatment

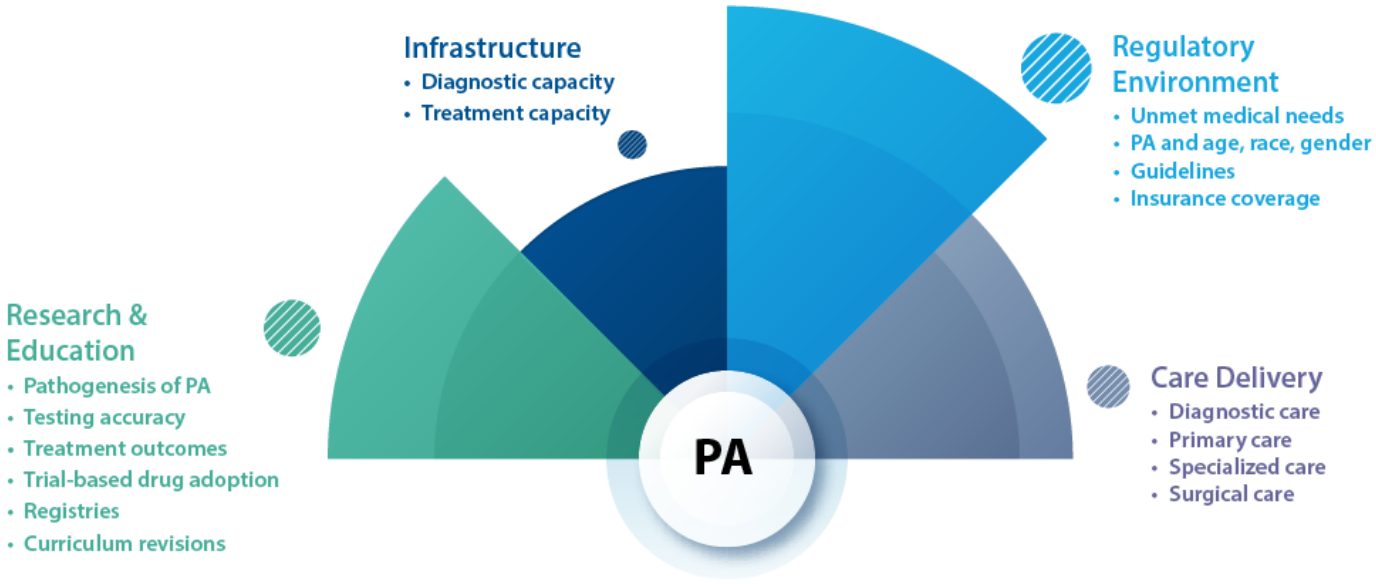
I wanted to get pregnant, and so I tried being off spironolactone during that time (about a year). I became sicker, so my physician and I decided it was unsafe to be off medications any longer. I also discovered that I had PCOS and was reproductively challenged due to this disease. I went back on spironolactone.

I am now on 150mg of spironolactone. Quality of life now, on this medication, is better for me. I sleep okay and magnesium supplementation has been very helpful with my sleep. I avoid alcohol and high sodium foods. My potassium level sits at 4.5, a good place for me and how I feel. I feel well-controlled, but some days it is still a struggle, not only physically but emotionally as well, and my stomach issues continue. If something stressful happens, my adrenaline increases and I feel very “hyped up.” I have to closely manage stress by avoiding those difficult situations as much as possible. PA is “a silent disease,” as it took doctors what feels like my whole life to find it. I don’t think as much damage would have been done to my body if it had been diagnosed ten years earlier when I first had symptoms.

Problem Dimensions

Issues with the magnitude of PA result from limitations within each of the key dimensions of healthcare, from the regulatory environment to research and education, care delivery, and infrastructure.

Successfully addressing those limitations requires prioritizing their contributing factors, and deploying multiple solutions on multiple fronts in a concerted way.



PA's "11 Factors"

Not only are most patients with PA undiagnosed, the above story summarizes what most diagnosed patients experience: an unnecessarily challenging and onerous journey to diagnosis completed in a piecemeal fashion over the course of many years, if not decades. Remediating such deficiencies requires addressing a series of factors found across the healthcare system.

1) Public Health

Because of the sheer number of affected adults, organizations accustomed to handling public health issues at scale need to support interventions. Being progressive in nature, PA goes particularly unnoticed in younger individuals who would benefit the most from early detection. Due to genetic causes and healthcare inequities, PA disproportionately affects individuals of African descent. Similarly, the disease disproportionately affects women (i.e., pregnancy, menopause). Yet, the diagnosis and treatment of PA are age-, race- and gender-agnostic. Prioritizing these population segments should be at the core of any public health program.

2) Insurance Coverage

The costs associated with near absence of diagnosis and treatment by far exceed that of adequate handling of the disease. However, if physicians were to diagnose and treat all affected patients, current payment structures would not allow for procedures such as adrenal venous sampling to be performed on the needed scale.

3) PA Guidelines

Although PA guidelines are readily available, their adoption is poor, even in academic medical centers. Uptake by practitioners would benefit from timely updates and an emphasis on knowledge translation to address issues such as signs and symptoms, renin and aldosterone testing interpretation, importance of and ways to achieve PRA > 1 µg/L, the benefit of dietary sodium restriction, management of the comorbidities associated with bilateral disease, and appropriate follow-up post-adrenalectomy to document state of improvement or cure.

4) Research

Considering the magnitude of the issues, research funding is largely insufficient, and should instead be proportional to the number of affected patients. Moreover, research needs to be prioritized to improve understanding of the disease, and devise more effective ways to diagnose and treat it. At a minimum, priorities should include testing performance and standardization, development of algorithms to identify patients with unmet medical needs, establishment of interoperable registries, timely and effective knowledge translation, and adoption of any and all relevant drugs based on standard clinical trials instead of reliance on off-label prescribing.

5) Medical Education

As of 2022, medical students are taught that PA is rare when the opposite actually is the case. The curriculum needs to be revised at all medical teaching institutions for resident and fellowship training in appropriate specialty and primary care disciplines.

6) Primary Care

Hypertension is mostly diagnosed and treated at the primary care level where initial screening for PA is expected to take place. Multi-stakeholder dialogue must be initiated to identify barriers to diagnosis, and co-create inclusive solutions that will facilitate screening and address patients' unmet medical needs.

7) Specialized Care

Diagnosis and treatment initiation rely on specialized care (i.e., endocrinology, nephrology, cardiology). Patients' lived experience attests to inadequacies along the diagnostic journey. Unavailability of specialized procedural and surgical care and uncoordinated treatment of comorbidities associated with bilateral disease are also widely reported. Practice networks linked to a referral center of excellence at their core need to be established to properly diagnose and treat newly screened patients, and to train caregivers as "PA champions" who will in turn grow such networks and increase the capacity for timely and high-quality care.

8) Diagnostic Ancillary Care

Adrenal venous sampling is the only means available to identify individuals who could benefit from curative surgery. Patients' lived experience attests to limited access to experienced interventional radiologists who can perform this procedure, inconclusive results and the need for repeat procedures. Interventional radiology should be an integral part of the practice networks described above if timely and effective testing is to be provided at scale.

9) Screening

As of 2022, ARR assays continue to vary across laboratories, and do not take age, race or gender into account. Widespread screening is unlikely to be successful unless such limitations are addressed. Guidance with test preparation and results' interpretation is equally needed. Moreover, testing of potassium levels needs to be performed accurately, and testing devices optimally developed to enable home testing by patients.

10) Infrastructure

Considering disease prevalence and current state of diagnosis and treatment, substantial increase in capacity is required at all medical centers in order to address unmet medical needs according to standards of care regardless of patients' geographical location.

11) Implementation Research

Implementation is the act of carrying an intention into effect (Peters et al., 2013). Granted that concerted intent emerges, issue resolution remains contingent upon successful implementation. The ability to inform decision making with regard to design, deployment and evaluation of interventions is therefore a contributing factor in itself, starting with the capacity to establish the needed structure to coordinate efforts (e.g., prioritization of factors, efficacy and sustainability of chosen interventions).

Conclusion

The factors affecting PA's standards of care are not uncommon. Diseases equally or more severe than PA have exhibited similar patterns in the past (e.g., familial hypercholesterolemia, type 1 diabetes). However, these disorders were less prevalent than PA, and none were mistakenly classified as "rare." Moreover, seldom did their standards of care remain inferior for such a prolonged period of time (i.e., over 60 years).

Whenever undertaken, successful transformation of landscapes similar to PA relied on the following dimensions:

- **Prioritized interventions:** if widespread screening was an indispensable step, it was progressively and systematically implemented after proper identification of unmet medical needs. Furthermore, its feasibility was supported by satisfactory testing performance and sufficient capacity to provide the needed diagnostic care. Precautionary measures such as ensuring availability and quality of care were also taken with regard to treatment. Failure to do so would have had harmful consequences, either by maintaining the status quo or by hastening interventions when readiness was lacking.
- **Collaborative work:** integrating activities and knowledge through shared authority and responsibility has been shown to improve health outcomes, morbidity and mortality (Morley & Cashell, 2017). Collaborative work is particularly relevant when scaling up diagnosis and treatment of overlooked disorders since this can only be achieved by system-wide integration of skills, processes and structures. No more than 1% of individuals with familial hypercholesterolemia were diagnosed in the United States in 2011. Together with the medical, research and patient communities, the Family Heart Foundation has increased that rate to 20% over the past 10 years.

In light of the 11 factors described above, and considering that PA is highly prevalent and treatable, improving the disease's standards of care is a necessity whose time has come.

Building on lessons learned from those who preceded them, the Primary Aldosteronism Foundation places a call to action to create a multi-disciplinary stakeholders' alliance based on shared commitment and inclusive partnerships to implement the patient-centered interventions that will lead to the diagnosis and treatment of PA at scale.

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