An in-depth investigation into journeys of patients diagnosed with Transthyretin Amyloidosis, Acute Hepatic Porphyria and Primary Hyperoxaluria Type 1

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Project Background

In the United States, rare disease affects 1 in 10 people [1, 2, 3]. The average time to diagnosis is about 4 to 5 years, though it can take as long as 30 years depending on the condition [4, 5]. Besides medical suffering, patients with rare diseases cost health systems an excess of ~$28,000 in additional direct medical cost per year in comparison to patients without rare disease [3]. Prompt diagnosis and appropriate management largely depend on proximity and access to quaternary specialty care, meaning rare disease disproportionately affects patients from underserved communities. We can't expect healthcare providers—even specialists—to be experts in managing and diagnosing all 10,000 currently known rare diseases. This is the problem Project Zebra set out to solve.

Project Objectives

This two-phase project leverages ZebraMD's proprietary platform and health system databases to independently review existing diagnosed patients, relevant disease guidelines and reputable literature to develop point-of-care clinical decision support ("CDS"). The CDS was utilized in two health systems to improve management of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), transthyretin amyloid cardiomyopathy (ATTR-CM), acute hepatic porphyria (AHP), and primary hyperoxaluria type 1 (PH1) to improve overall patient outcomes. Phase 1 analyzed patient journeys from deidentified aggregated meta data from existing diagnosed patient cohorts of the four disease states at the University of California, Los Angeles (UCLA) and the University of California, San Francisco (UCSF). Phase 1 aimed to evaluate where in the patient journey implementation of ZebraMD's CDS tool would be most effective, and what features would be needed to bridge current gaps in clinical care. Healthcare utilization trends were determined by how often encounter departments show up in the data for patients in each given disease state (ie, most requently seen encounters per patient with that disease state). Phase 2 assessed how point-of-care interventions at key stages of the patient journey (identified in Phase 1) influence clinician behavior and served for ZebraMD as a prototype for a scalable "Best Practice Alert (BPA)." The prototype aided development of a future automated CDS tool and Artificial Intelligence (AI) assistant summarizing and personalizing the current treatment guidelines for rare diseases. In Phase 2, point of care management recommendations were displayed on the ZebraMD webapp outside of the EHR and necessitated manual inputting of either the disease name, international classification of diseases (ICD) code or genetic variant. In Phase 2, physician specialists in relevant departments utilized the ZebraMD application at the point of care for patients with any of the four disease states and provided feedback afterward. The project primarily engaged physicians with deep expertise in the four disease states for app feedback, but the project was also discussed at monthly primary care and clinical informatics meetings at UCLA and UCSF to collectively obtain feedback on technical, logistical, and real-world practice considerations for EHR implementation. ZebraMD collected data objectively via user metrics and subjectively by a user survey attached to each use case (Appendix 1).

Phase 1 Results

Hereditary Transthyretin Amyloidosis with polyneuropathy (hATTR-PN)

Demographics

A total of 59 patients (51 at UCLA and 8 at UCSF) were analyzed across both academic centers; patients analyzed had both positive genetics and clinical symptoms. The majority of patients fell within the 60+ age range (94% at UCLA and 55% at UCSF) (Appendix 6). At both institutions, <30% of diagnosed hATTR-PN patients were from lower socioeconomic backgrounds, perhaps indicating that diagnoses are more commonly made in higher socioeconomic

background brackets. Additionally, these same patients from lower socioeconomic backgrounds had the longest diagnostic delay and were less likely to be prescribed a disease-specific therapy (orphan drug). Across both institutions, similar patterns were observed in terms of gender, race and ethnicity demographics, showing roughly equal distribution between male and female patients (57% vs 43%, respectively), with White patients being a majority (>50%).

Insurance

At UCLA, Medicare was the most common payor followed by Preferred Provider Organization ("PPO") (80% and 67%, respectively).* A portion of patients payed out of pocket (33%), meaning that they covered some proportion of their care 'out of pocket,' particularly in cases where insurance may not cover 100%. At UCSF, a large majority of patients used Medicare Fee-for-Service ("FFS") (42%) and additionally payed a certain amount out of pocket, likely because some parts of the disease-specific healthcare were not covered by insurance, or the patient did not need to use insurance, or there may be a co-pay or co-insurance payment the patient was liable for.

**Percentages occasionally exceed 100% because a patient can have more than 1 insurance in the data (eg, if the insurance changes during the year, 2 insurances will be listed for that year).*

Healthcare Utilization

Healthcare utilization patterns revealed that patients pre-diagnosis frequently received evaluations for suspected HIV infections–although more so in the ATTR-CM cohort (17%) than the hATTR-PN cohort (10%)-and evaluations for suspected autoimmune disease treated with steroids, particularly in the West Coast hATTR-PN patient population. Interestingly, qualitative physician feedback revealed Chronic Lyme Disease as a symptomatic mimicker of hATTR-PN pre-diagnosis on the East Coast. Within the hATTR-PN patient cohort, the most common healthcare encounter observed was Neurology Outpatient Clinic (75%), followed by Neuromuscular Subspecialty Clinic (62%), General Cardiology (37%), Hematology/Bone Marrow (38%), and Advanced Heart Failure Subspecialty Clinic (25%).

Management

FDA-approved medications for hATTR-PN were most frequently prescribed by Neurology, Cardiology, and Primary Care. Interestingly, patients who were not prescribed a disease-specific therapy were more likely to be on ocular and oral steroids, whilst patients who were prescribed disease-specific therapies were more likely to have undergone a formal biopsy for diagnosis.

Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM)

Demographics

The cohort analysis found 104 total patients between the two health institutions (86 at UCLA, 18 at UCSF). At both institutions, ATTR-CM disproportionately affected males (>67% confirmed male cases at UCLA, 85% confirmed male cases at UCSF). Additionally, age dispersion at UCLA and UCSF indicated a majority of patients fell in the 60+ year age group (80% and 94%, respectively). Moreover, in comparison to the hATTR-PN patient cohort, nearly 50% of all ATTR-CM patients at UCLA ranked in the lower third of socioeconomic class. In terms of Social Vulnerability Index (SVI) scoring at UCLA, 48% of patients fell into moderately to highly vulnerable socioeconomic categories (SVI >0.6) with 37% of patients in the highest vulnerability range (SVI 0.8-1). However, socioeconomic SVI was more evenly spread across lower ranges (0-0.6), while total SVI skewed higher (0.8-1), indicating that socioeconomic factors don't fully explain overall patient vulnerability. At UCSF, patients who were from lower Area Deprivation Index (ADI) categories were more likely to be prescribed disease-specific medicines ("DSMs"), meaning that those from higher socioeconomic backgrounds were more likely to be prescribed the medications to manage their disease.

Insurance

At UCLA, Medicare and Commercial were the most common payors (80% and 67%, respectively).* At UCSF, Medicare FFS was the most common payor (75%) followed by Commercial (30%).* All patients contributed at least some amount out-of-pocket.

Healthcare Utilization

At UCLA, before prescription of DSMs, patient records showed high engagement from Cardiology, Neuromuscular, and Pathology departments, with moderate engagement from Neurology and specialized services. Similarly, at UCSF, trends showed high involvement from the Cardiology department with moderate engagement from Neurology, Neuromuscular, and specialized services. Following the prescription of DSMs, trends at UCLA and UCSF were consistent, demonstrating increased engagement from high-involvement departments, with an overall trend towards broader multidisciplinary

involvement. Finally, the most frequently ordered lab tests at UCSF were metabolic panels, immunohistochemistry tests, complete blood count ("CBC"), and cardiac biomarkers.

Acute Hepatic Porphyria (AHP)

Demographics

A total of 87 patients (69 at UCLA and 18 at UCSF) were analyzed across both academic centers. When comparing SVI and ADI between UCLA and UCSF cohorts, there was no observed difference between patients being prescribed different FDA-approved medications for AHP at either UCLA or UCSF.

Insurance

At UCSF, the most common insurance type was Commercial (59%), followed by Medicare FFS (34%). Almost all patients had out-of-pocket costs, with Worker's Compensation being rare (<2%). Similarly, at UCLA, Commercial (50%) was the most common insurance type, followed by Medi-Cal (25%).

Healthcare Utilization

In the UCSF cohort, the departments most frequently seen were Hepatology, Infusion OP, ED, Pain Medicine, Acute Care and General inpatient (IP) wards, and Gastrointestinal (GI) general. Key management trends for patients with AHP at UCLA showed general initial labs (comprehensive metabolic panel, CBC, urinalysis, glycated hemoglobin) and imaging (electrocardiogram, ultrasound, magnetic resonance imaging (MRI), chest X-rays) prior to diagnosis. Following diagnosis, general labs and imaging included delta-aminolevulinic acid (ALA) and iron tests (iron studies in relation to hemin administration) and brain MRIs, likely related to seizures and neurological deficits that can be seen in AHP patients.

Management

The Acute Hepatic Porphyria review showed a large percentage of patients >60 years of age still experiencing severe AHP symptoms. This potentially indicates that symptoms can continue post-menopause or peri-menopause and providers should not assume symptoms will lessen after menses cease. At UCSF, when observing the cohort of AHP patients with records in Medications (n=18), 67% received FDA-approved disease-specific medications. Finally, typical chief complaints for patients not on any DSM included abdominal pain (71%), seizures (14%), nausea (14%), back pain (14%), lethargy (14%).

Primary Hyperoxaluria Type 1 (PH1)

Due to Institutional Review Board related reasons, only data from patients above the age of 18 was included for this analysis.

Demographics

A total of 104 patients (28 at UCLA and 76 at UCSF) were analyzed across both academic centers. At UCSF, the highest percentage of PH1 patients identified as White (60%) followed by Asian (13%). Only 3% of all patients identified as Black or African American. Gender demographics showed a relatively even split between male and female patients (43% versus 57%, respectively). Lastly, age dispersion demonstrated the higher proportion of patients were above the age of 60 (42%) followed by those aged 18-20 (27%).

Insurance

At UCSF, the most common payor was commercial (64%) followed by Medicare (25%). Similar trends were observed in the UCLA cohort, with Commercial being the most common payor (81%), followed by Medicare (33%).*

Healthcare Utilization

PH1 patients at both UCLA and UCSF were most frequently first encountered in primary care and then referred to hematology-oncology for abnormal CBC results, indicating that this basic lab could be the first abnormality seen as a sign of their disease. The subsequent referrals from primary care to hematology indicate that basic anemia testing alone was not able to determine a cause for the low blood count, triggering a referral to a specialist. As expected, the highest hospitalization rates among all PH1 patients was observed in the 18-20 year age range, though no other significant differences in healthcare encounters were noted in this age group.

Management

Importantly, no observed differences were noted in terms of age and gender for patients being prescribed DSMs. In addition to FDA-approved medications for PH1, other common prescriptions included nausea medications, procedural pain medications, and fluids.

Phase 2 Results–User Feedback

Physician Feedback

The physician feedback survey received 28 responses via the ZebraMD web app. Over 300 unique searches for symptom combinations or rare diseases have been logged. Among web app survey

respondents, the most common clinical specialties were family medicine (22%) and internal medicine inpatient physicians (22%) (Figure 1). A plurality of respondents (33%) reported that the web app tool had changed their clinical decision making (Figure 2). Among 6 respondents who reported changing their clinical decision making, 3 reported changes to treatment decision making—2 to referrals, and 1 each to diagnosis and clinical management. Respondents were equally divided on whether the web app tool had provided them with new information that they did not previously know. Importantly, the ZebraMD team had shared the app with specialist physicians who frequently treat these rare diseases (hATTR-PN, ATTR-CM, AHP, PH1), and are thus considered experts in the field. Any new information made available to these specialist physicians was considered a positive outcome (Figure 3).

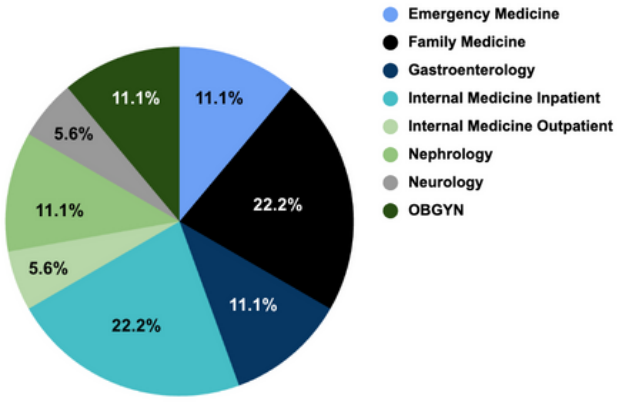

FIGURE 1. Reported clinical specialties among physician user survey respondents (n = 18). Abbreviations: OBGYN, obstetrician/gynecologist.

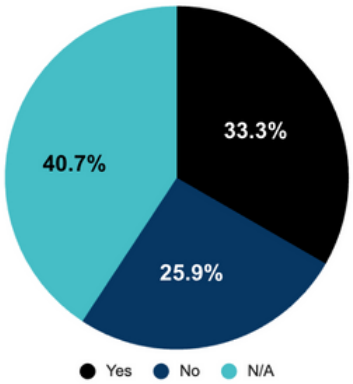

FIGURE 2. Reported changes to clinical decision making after using the web app tool (n = 27).

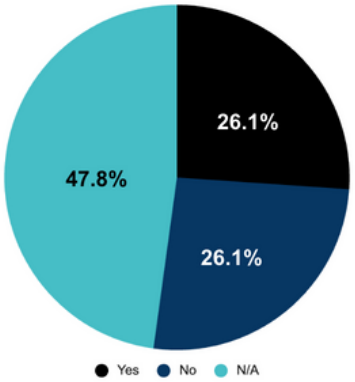

FIGURE 3. Physicians reporting whether the web app tool provided new information not previously known (n = 23).

In addition to the user survey feedback, substantial qualitative feedback was collected from physician discussion groups (Table 1). One specialist physician noted the utility of the web application to narrow down the list of possible diseases, thereby reducing the number of screening tests required. Generalist physicians appreciated the application's integration with other resources, including clinical trial information, local specialist referrals, ordering panels, and financial assistance programs. Physicians were curious about adapting the tool for their specific departments, enabling direct patient use, tracking orders, and identifying gaps in care. Additionally, physicians suggested that the ZebraMD tool would be valuable for community health programs and may benefit from further automated message alerts to relevant care team members after care visits. In further discussions, physicians emphasized that the app should also be made available to medical assistants and nurses as they often spend the most time with patients and handle preparatory work, preauthorizations, and orders.

There was a concern (raised by specialist physicians) that the ZebraMD tool may increase referrals to specialists who are already overburdened. Therefore, it is crucial that the application assists specialist workflows by providing quick synopses of likely rare diseases, test panels required, and links to supporting resources. In under-resourced communities, this may require partnerships with telehealth companies to ensure access to appropriate specialists.

Table 1. Qualitative feedback from physician discussion groups

Abbreviations: EHR, electronic health record; PCP, primary care physician.

Physician Specialty	Feedback / Direct Quote
Cardiology	"Very helpful for us as subspecialists to have a better idea of what testing to start with, it narrows things down with probabilities, rather than ordering extensive screenings on everyone."
Family Medicine	"The prevention screening recommendations are great but also a brief synopsis of what the disease is."
Family Medicine	"Good to have the local referral in there because then I know where to send them to."
Internal Medicine	"The direct links to ordering panels is helpful especially because I am not an academic physician and do not have access to a Genetics department."
Hematology Oncology	"The clinical trials feature is my favorite."
N/A	"Didn't know there were financial assistance programs for therapeutics readily available."
Family Medicine	"Can I adapt this to primary care?"
Internal Medicine	"Can we make care gaps and pend orders for these patients?"
Neurology	"Can we make this for long term care facilities?"
Clinical Informatics	"Can patients use this too?"
Neurology	"Would be best for community programs."
Emergency Medicine	"Would be good to have an after-visit in-basket message to PCP in addition to the alert in the EHR."

Key Learnings

Results from the Phase 1 cohort analysis and Phase 2 physician feedback survey indicate that ZebraMD's technology may have the most impact by reducing the delay to trigger a referral in a community setting, not quaternary academic centers, which are often the end stage of the diagnostic journey [6, 7, 8]. Therefore, it is essential to collect feedback and investigate logistics of implementation in "front-line departments" such as the Emergency Department (ED) and primary care in the community setting. The ability to start a workup within primary care, thereby having crucial labs and/or imaging taken in the interim before a patient sees the specialist, is key. This has been amended in ZebraMD's strategy and best practice alert contents (Appendix 2, 3, 4). Primary care physicians also requested ongoing management items post-diagnosis that can be actioned in their department to minimize patient travel for ongoing specialist appointments, such as targeted education, relevant links, and making resources directly available in the EHR via order suggestions. Specialists expressed difficulty staying current on disease-specific medications and selecting the best option for each patient. They appreciated automated BPAs and in-basket updates with the latest guidelines pre and post clinic visit. On the technical side, the cohort analyses identified the key Epic (EHR) data fields ZebraMD's technology must read to supply information for precision-management algorithms for diagnosed patients and prediction algorithms for undiagnosed patients.

References

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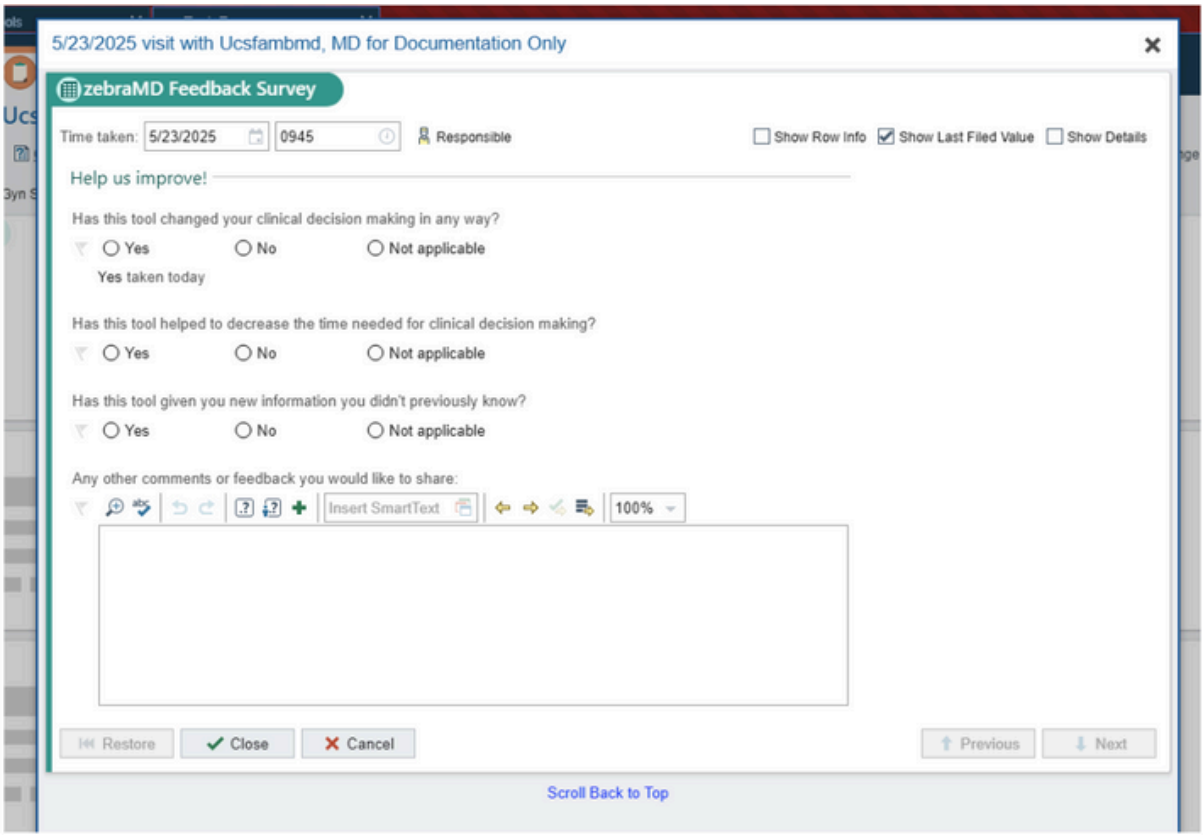
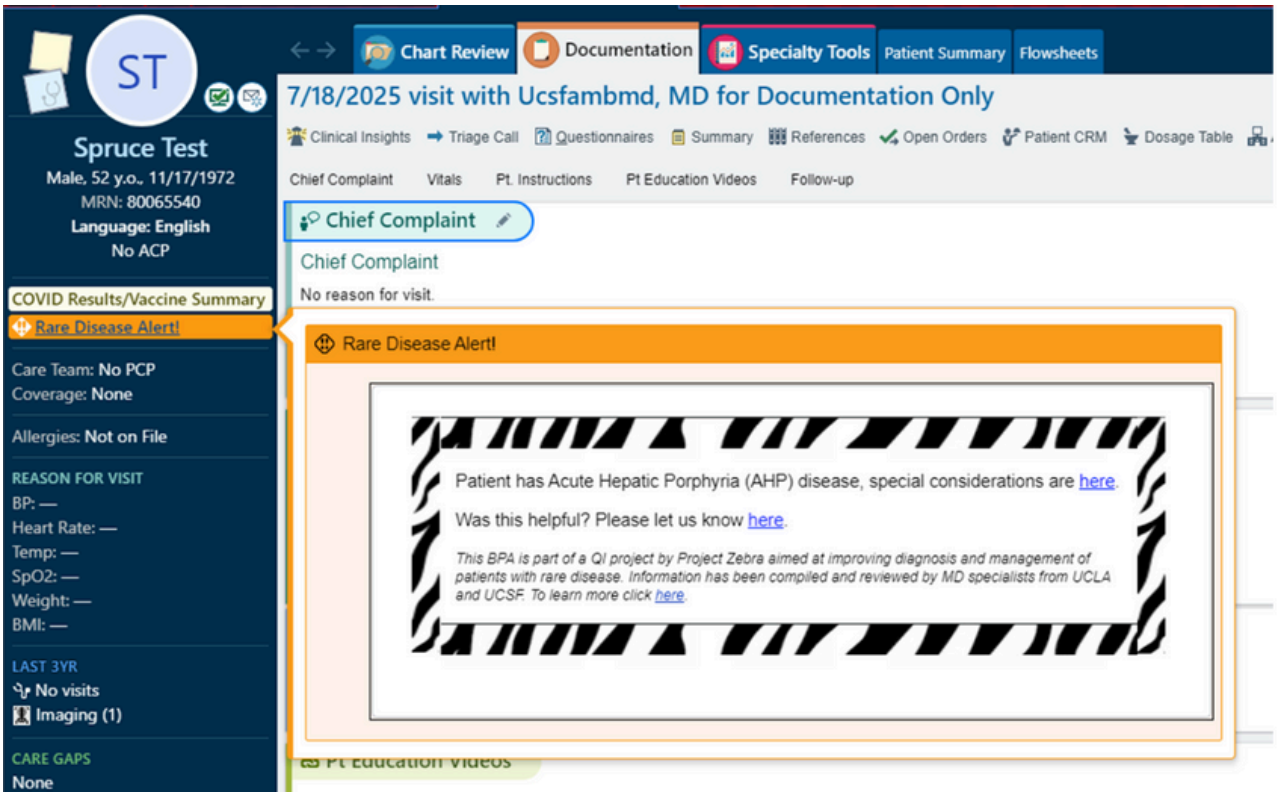
Appendix

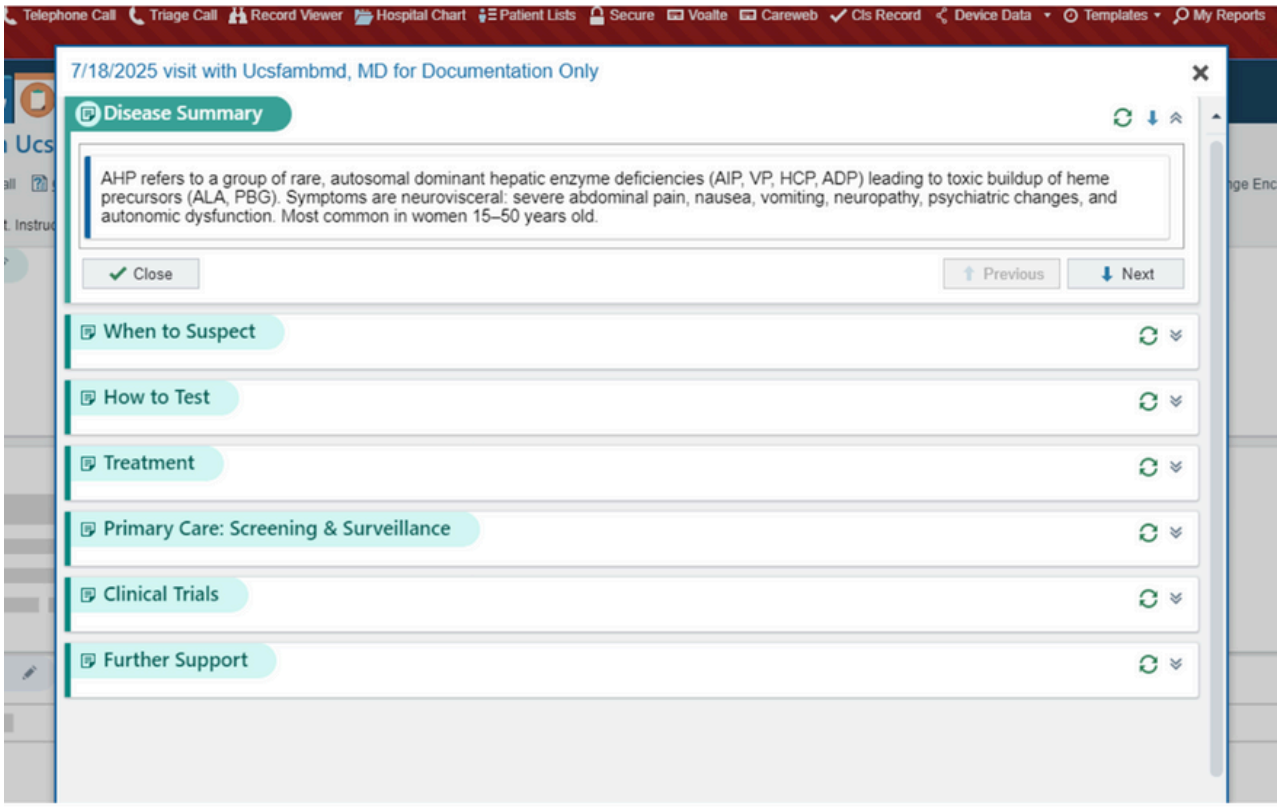
Appendix 1. User feedback survey from web application



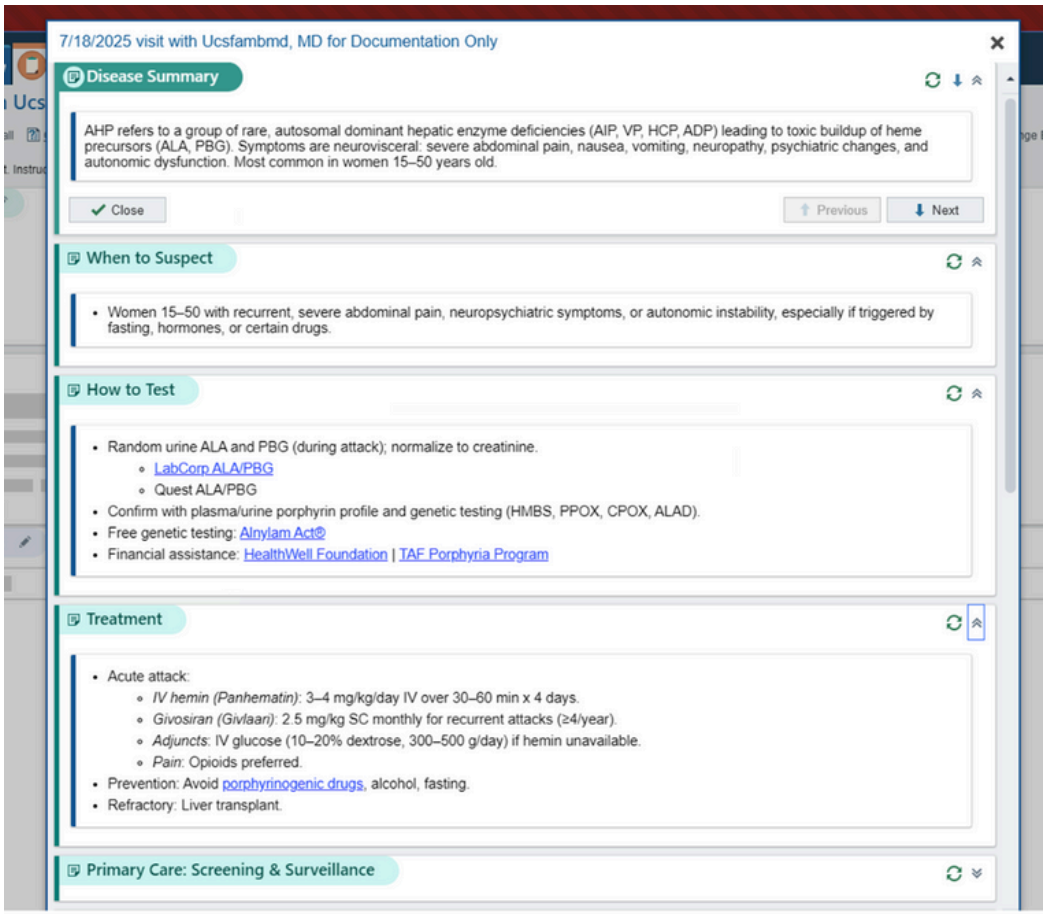
Appendix 2. Example best practice alert (BPA) for acute hepatic porphyria



Appendix 3. Example clinical information summary for acute hepatic porphyria (AHP)



Appendix 4. Example links to useful resources for acute hepatic porphyria (AHP)



Appendix 5. Key Definitions

- Disease Specific Medicine (DSM): In the context of this White Paper, a DSM is any FDA-approved medication and/or drug designed to be prescribed to individuals with a particular disease or genetic condition.

- Whole Cohort: Includes all patients with the disease-specific ICD code listed. Patients have been worked up for the disease but never received positive genetic tests OR have a variant of uncertain significance OR have an external workup done that did not translate into the UCLA or UCSF system.

- Confirmed Cohort: Includes patients with positive genetic tests and clinical symptoms present.

- Social Vulnerability Index (SVI) Score: The SVI scoring system is utilized at UCLA, measured on a scale of 0.0-1.0, with 0.0 being least vulnerable and 1.0 being most vulnerable. SVI refers to the demographic and socioeconomic factors (such as poverty, lack of access to transportation, and crowded housing) that adversely affect communities that encounter hazards and other community-level stressors. These stressors can include natural or human-caused disasters (such as tornadoes or chemical spills) or disease outbreaks (such as COVID-19).

- Area Deprivation Index (ADI) Score: The ADI scoring system is utilized at UCSF, measured on a scale of 1-100, with 1 being least deprived and 100 being most deprived. ADI displays the relative socioeconomic conditions of neighborhoods. ADI is created from publicly-available data in theoretical domains of income, education, employment and housing quality. Areas with greater socioeconomic disadvantage are ranked higher.

Appendix 6. hATTR-PN Age Dispersion

Age Range	Whole Cohort	Confirmed Cohort
0-20	1 (0.3%)	N/A
20-40	5 (1.3%)	N/A
40-60	18 (4.8%)	1 (12.5%)
60+	351 (93.6%)	7 (87.5%)

UCSF Age Dispersion

Age Range	Whole Cohort	Confirmed Cohort
0-20	6 (5.1%)	2 (4.0%)
20-40	15 (12.7%)	5 (10.0%)
40-60	32 (27.1%)	17 (34.0%)
60+	65 (55.1%)	26 (52.0%)

UCLA Age Dispersion

This white paper has been sponsored by Alnylam Pharmaceuticals