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Diagnostic Pathways, Genetic Testing, and Impact of COVID-19 on Patients in Europe with X-Linked Retinitis Pigmentosa: Results From the Cross-Sectional EXPLORE XLRP 1 Physician Survey

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INTRODUCTION

- X-linked retinitis pigmentosa (XLRP), a form of inherited retinal dystrophy, is a rare eye disease associated with the progressive loss of photoreceptors. XLRP is among the most aggressive forms of retinitis pigmentosa, accounting for approximately 15% of all cases, leading to legal blindness in the third or fourth decade of life.[1-4]
  - As an X-linked recessive disorder, XLRP primarily affects men.[1, 3-6]
  - Women who are heterozygous for an XLRP mutation are often considered unaffected carriers and may be asymptomatic, but some female carriers can experience significant visual symptoms, a phenomenon thought to be related to variable X-inactivation patterns.[1, 3-9]
  - Approximately 70-80% of XLRP cases are caused by mutations in the *retinitis pigmentosa GTPase regulator* (RPGR) gene.[1-5, 8]
  - For inherited retinal diseases such as XLRP, genetic testing is strongly recommended to provide a definitive diagnosis.[10, 11]
- No treatment is currently available for XLRP. The recommended management includes use of low-vision aids, treatment of the complications (e.g., cataract, cystoid macular edema), and blindness rehabilitation strategies.[11-16]
- Limited published data are available that describe details of the XLRP patient journey (including assessment, genetic testing, diagnosis, and management); there is a need for a better real-world understanding of the current standards of clinical practice and the potential obstacles to diagnosis and genetic testing.
- As potential targeted therapies for XLRP emerge, early diagnosis and access to genetic testing for both patients and family members will likely be topics of key importance, as will efforts to streamline the patient journey. The EXPLORE XLRP 1 survey interviewed retina specialists (n=20) and geneticists (n=5) in Germany, France, Italy, Spain, and the United Kingdom (UK) to provide insights on patients with XLRP (n=80), to better understand the pathways by which patients in Europe with XLRP are referred to these specialists for diagnosis, and to examine the impact of COVID-19 on patient management.

METHODS

- EXPLORE XLRP 1 was an exploratory, cross-sectional, physician survey conducted in Germany, France, Italy, Spain, and the UK.
  - Retina specialists and geneticists in these countries were identified who had at least 5 years' experience managing or seeing patients with XLRP, and who were responsible for the recent management of patients with XLRP (retina specialists) or who were responsible for the genetic testing of patients with XLRP (geneticists).
- Retina specialists provided anonymized information for four recent patients diagnosed with XLRP (with or without genetic testing) from their practices or under their management, including details of the diagnostic and referral process and decisions to pursue genetic testing.
  - The anonymized patient information was collected through an online survey completed by the retina specialists and stored in a secure database.
  - Individual 60-minute telephone interviews were then conducted with the retina specialists and geneticists to capture their perspectives on management approaches for patients with XLRP.

RESULTS

- A total of 20 retina specialists and five geneticists from Germany, France, Italy, Spain, and the UK participated in the study (four retina specialists and one geneticist from each country). Patient information was collected for 80 patients (16 from each country).
- The retina specialists and geneticists interviewed reported that their patients with XLRP were mostly male (91%) and that 57% were aged 18-40 years.

Patient referral pathways

- The responses to the physician survey indicated that the pathways by which patients with XLRP are referred to retina specialists and geneticists in these five European countries can vary considerably by country **(Figure 1)**.
  - In Germany and the UK, patients see retina specialists/geneticists through multiple routes, including referrals by general practitioners, optometrists, and ophthalmologists.
  - In France, Spain, and Italy, patient pathways are more linear: most patients see retina specialists/geneticists as a result of referral by ophthalmologists.
- **The average time between the onset of symptoms and diagnosis also varied between countries. Physicians estimated that their patients experienced an average time of 4 years between the onset of XLRP symptoms and diagnosis, and that some patients experienced even longer delays (more than 10 years in some cases) (Figure 2).**

Figure 1. Patient referral pathways by country

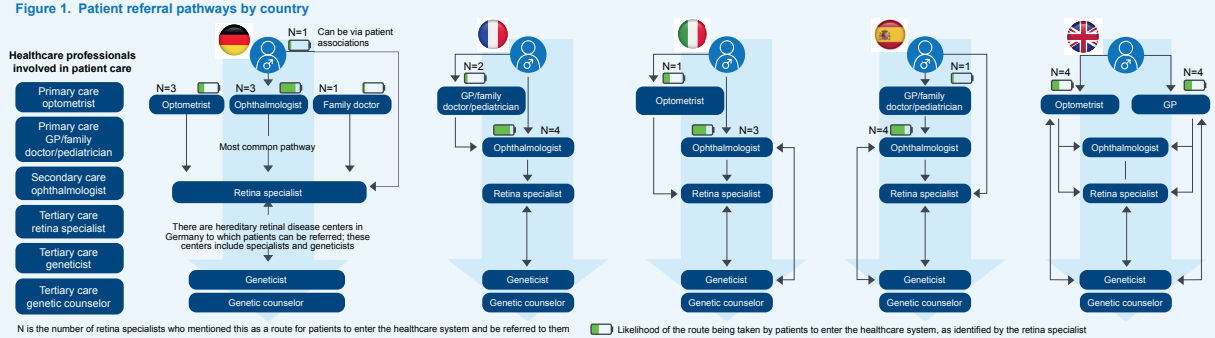
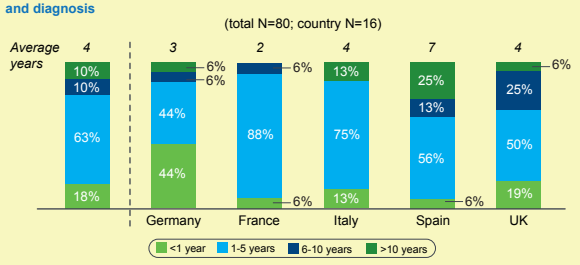


Figure 2. Time to diagnosis: average duration in years between the onset of symptoms and diagnosis

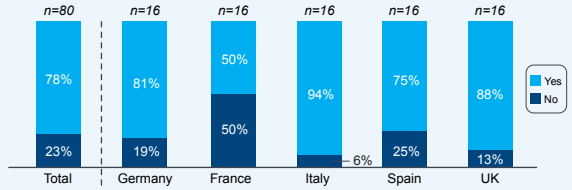


- Once diagnosed, patients are provided with information about the disease, how it progresses, and their prognosis.
  - Patients are encouraged to speak to a genetic counselor to understand the hereditary nature of the disease.
  - The importance of monitoring is highlighted, especially given the complications that can arise.
- Retina specialists reported seeing patients with XLRP typically once or twice a year for consultation.

Diagnosis and genetic testing

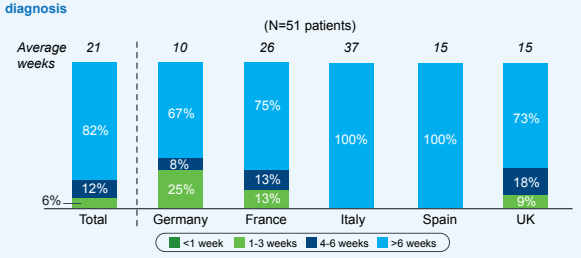
- The retina specialists interviewed indicated that more than half (58%) of their patients with XLRP were initially referred to the retina specialist without a specific suspicion of XLRP.
- Genetic testing was used as part of XLRP diagnosis in 78% of patients; among the five countries, the lowest rate of genetic testing (50%) was reported in France **(Figure 3)**.

Figure 3. Proportion of XLRP diagnoses confirmed with genetic testing



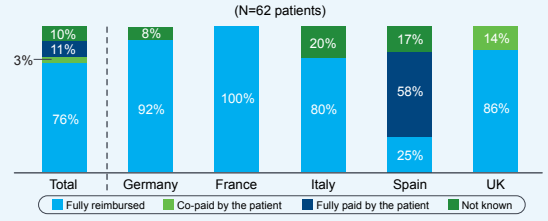
- Retina specialists reported that the majority of patients who had not undergone genetic testing were older than 40 years.
- Retina specialists estimated that it usually took longer than 6 weeks to receive the results of XLRP genetic testing, and some patients waited up to 6 months to receive test results **(Figure 4)**.

Figure 4. Average duration in weeks between samples being taken for genetic testing and diagnosis



- The costs of genetic testing are fully reimbursed for most patients in all countries included in the study, except Spain, where more than half of the genetic tests were paid for in full by patients. In the UK, testing costs were co-paid by 14% of patients **(Figure 5)**.

Figure 5. Reimbursement for the costs of genetic testing



- Before genetic testing was undertaken, key tools used to support XLRP diagnosis included optical coherence tomography, electroretinography, fundus autofluorescence, visual acuity testing, and static perimetry.
- Despite barriers to genetic testing (e.g., costs, long waiting times for results), physicians agreed that genotypic diagnosis is helpful for predicting disease progression and to allow patients the option of participating in clinical trials.
  - Additional perceived barriers to genetic testing included the distances some patients needed to travel, the fact that no treatment is available for the disease, and the concerns of some physicians regarding reliable identification of mutations by the tests.
- The clinical experts generally recommend that the family members of patients with suspected or confirmed XLRP should also be genetically tested.

Impact of the COVID-19 pandemic

- The COVID-19 pandemic led to a reduction in in-person clinic visits, which was thought to be a consequence of patients' fearing infection, as well as travel restrictions being imposed.
- HCPs are interested in solutions for remote management of patients, with some physicians having seen patients via video consultations.

CONCLUSIONS

- **Early diagnosis is important for patients to be able to better understand the impact of their diagnosis on their life and family, and also to allow them the option of participating in clinical trials.**
- **The pathways by which patients with XLRP in these five European countries visit retina specialists and geneticists are complex, lengthy, and vary considerably by country.**
- **XLRP diagnosis was confirmed by genetic testing for the majority of patients treated by retina specialists; however, long waiting times for test results accounted for incomplete uptake, especially among older patients.**
- **Tele-consultations and remote management have emerged as potential solutions for monitoring patients during the COVID-19 pandemic (and potentially beyond) and can reduce the travel burden for patients and their caregivers/supporters.**
- **Although this cross-sectional survey was exploratory in nature, it provides valuable real-world insights from retina specialists and geneticists that may not otherwise be available through clinical studies or health economic research and demonstrates that diagnosis, genetic testing, and management pathways can vary considerably among patients with XLRP.**

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Conflicts of Interest

KP, JL, TD, YK, and RN are employees of Janssen Pharmaceuticals, Inc. KA is an employee of IQVIA and has a consulting agreement with Janssen Pharmaceuticals, Inc. FP has received personal fees for advisory boards from Janssen.

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