Summary of the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome: an Australian perspective

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he 2023 International evidence-based guideline for the assessment and management of polycystic ovary syndrome project was led and primarily funded by Australia through the National Health and Medical Research Council (NHMRC) Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHiRL).¹⁻⁷ Responding to strong calls from patient and consumer groups, the guideline addresses a condition that affects one in eight Australian women, 140 million women globally, and is complex, underdiagnosed, undertreated, underfunded, underresearched, misnamed and misunderstood. 1-5,8-11 As a neglected women's health condition, polycystic ovary syndrome (PCOS) is relegated to brief education snapshots (usually under infertility), or no dedicated content in undergraduate health professional curricula. Individuals affected report limited knowledge and dismissive attitudes from health professionals (Box 1), despite the high prevalence, broad clinical features and marked impact on quality of life.¹⁻⁶ PCOS is also a misnomer as it is neither an isolated disease of the ovaries or involving true ovarian cysts.^{5,11} Rather, it is a genetic and lifestyle-related chronic endocrine condition with insulin resistance and hyperandrogenism and a myriad of reproductive, psychological, cardiometabolic and dermatological features. ^{6,12,13} To address these challenges and in response to both patient and health professional priorities, we aimed to engage internationally and develop and translate comprehensive evidence-based guidelines for diagnosis, assessment and treatment, to improve the lives of individuals with PCOS worldwide. Here, we outline the process and key recommendations, applying an Australian lens.

Methods

Guideline development

The guideline development process was overseen by international advisory and management committees, guideline development groups (GDGs) and paediatric, consumer and translation committees. Participants were nominees of CRE WHiRL, international co-funding partners (the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology) and 35 collaborating professional and consumer organisations, including ten from Australia. Guideline scope and clinical question prioritisation were derived from consumer input based on the public participation spectrum framework, formative research, all global survey of more than 750 women, and involved experts.

Evidence scoping and allocation

The evidence team, led by AM and CTT and supported by HJT, established, trained, supervised and mentored 26 early-career

Abstract

Introduction: The Australian-led 2023 International evidence-based guideline for the assessment and management of polycystic ovary syndrome was based on best available evidence, clinical expertise and consumer preference. It followed best practice, involved extensive evidence synthesis and applied relevant frameworks across evidence quality, feasibility, acceptability, cost and implementation. Thirty-nine societies and organisations covering 71 countries were engaged. The evidence in the assessment and management of polycystic ovary syndrome (PCOS) has generally improved in the past five years, but remains of low to moderate quality. The technical evidence report, 52 systematic reviews and analyses (approximately 6000 pages) underpin 77 evidence-based and 54 consensus recommendations, with 123 practice points.

Main recommendations: Changes include:

- refinement of individual diagnostic criteria, a simplified diagnostic algorithm and inclusion of anti-Müllerian hormone levels as an alternative to ultrasound in adults only, and differentiation of adolescent and adult criteria:
- strengthening the recognition of broad features of PCOS including metabolic effects, cardiovascular disease, dermatological symptoms, sleep apnoea, a high prevalence of psychological features and a high risk of adverse pregnancy outcomes;
- emphasising the poorly recognised, diverse burden of disease, the vital need for greater health professional education, evidence-based patient information, improved models of care, shared decision making and research efforts to improve patient experience:
- maintained emphasis on healthy lifestyle, emotional wellbeing and quality of life, with awareness and consideration of weight stigma; and
- emphasising evidence-based medical therapy and cheaper and safer fertility management.

Changes in management as a result of this guideline: The 2023 guideline is approved by the National Health and Medical Research Council and provides clinicians and patients with clear advice on best practice in a common and neglected condition, based on the best available evidence, expert multidisciplinary input and consumer preferences. It provides vital, extensive patient and provider resources to enhance evidence-based care.

The full guideline is available at www.monash.edu/medicine/mchri/pcos/guideline.

researchers in a network recruited from engaged organisations and GDG affiliations to undertake systematic reviews. Guideline methods aligned with best practice NHMRC requirements and the Appraisal of Guidelines for Research and Evaluation-II (AGREE-II) tool as documented in the full guideline and technical report. Comprehensive evidence

1 Lived experience of PCOS

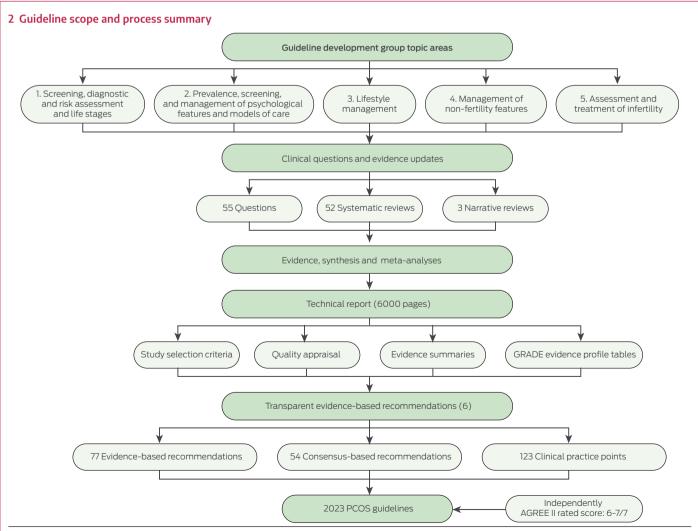
Lorna Berry, who has polycystic ovary syndrome (PCOS), was one of the lived experience experts on the guideline. Here she shares her journey, highlighting the challenges in obtaining a diagnosis and reliable information, which greatly impacted her wellbeing, mental health and fertility options. She firmly believes that no woman should go undiagnosed and unsupported.

I fought for my PCOS diagnosis, being repeatedly dismissed by health professionals. PCOS affected all aspects of my life, family, fertility, wellbeing and lifestyle. Living with PCOS is challenging enough, but the struggle to find reliable information feels like an uphill battle. It's disheartening when every corner you turn, there's someone trying to sell a miracle cure. I need trustworthy information that deals with my concerns and answers my questions and empathetic, knowledgeable health professionals who take this seriously to avoid the frustration and sense of hopelessness that can go with having PCOS. Empowering women so they can advocate and partner with and educate doctors and other health professionals is of utmost importance. We need to make sure that the next generation doesn't go undiagnosed and unsupported.

synthesis involved 52 systematic reviews and generated new evidence from extensive meta-analyses. Study inclusion was determined from *a priori* population, intervention/exposure, comparison, outcome (PICO/PECO) frameworks.⁶ Databases (including CINAHL and MEDLINE, MEDLINE In-Process and other non-indexed citations, PsycINFO, EMBASE and All EBM Reviews via OVID) were searched for published, English language articles. Titles, abstracts, keywords and full texts were screened and the evidence team, GDG clinical leads and evidence experts were engaged throughout (Box 2).⁶

Study-level method quality was assessed with a risk of bias rating of low, moderate, high or insufficient information. Evidence certainty was determined at the outcome-level using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence to decision framework, across risk of bias, inconsistency, indirectness, imprecision and other bias (eg, publication bias) as documented in the technical report. Critical outcomes were determined by GDG clinical leads and consumers and influenced overall certainty of evidence.

To ensure authenticity and accuracy of evidence, the Research Integrity in Guidelines and evIDence synthesis (RIGID) framework²⁰ was developed, with study level integrity



AGREE-II = Appraisal of Guidelines for Research and Evaluation-II tool; GRADE = Grading of Recommendations, Assessment, Development and Evaluation framework; PCOS = polycystic ovary syndrome.

scores using the TRACT tool,²¹ and an integrity committee for consensus on study allocations. Authors of studies with moderate and high risk of integrity concerns were contacted. All scores and reasons were tabulated in the technical report.⁶ Data were extracted into evidence summary templates, with meta-analyses done using Review Manager or STATA. Statistical heterogeneity was assessed using I^2 and explored via sensitivity analysis and subgroup analyses, where possible.

Clinical leads drafted recommendations, refined at face-to-face meetings using the GRADE framework, across certainty, quality, feasibility, acceptability, cost and implementation. With clinical and consumer input, recommendations and strengths were determined. The evidence quality was improved from the 2018 guidelines but was generally low-moderate quality. Overall, the guideline development process resulted in 52 systematic reviews and analyses, 77 evidence-based and 54 consensus recommendations, with 123 practice points. The draft guideline was externally reviewed via public and targeted consultation of engaged organisations, including consumer groups. Adaptations occurred in response to national and international public consultation and peer review. After meeting the standard for clinical practice guidelines, the guideline was approved by NHMRC in July 2023 (Box 2).

Recommendations

Diagnosis and history

The updated recommendations emphasise the importance of diagnosing PCOS according to international, evidence-based guideline criteria, 22 building on consensus-based Rotterdam criteria.²³ The presence of at least two of the following points is required in adults: (i) clinical or biochemical hyperandrogenism, (ii) ovulatory dysfunction or irregular cycles, and (iii) polycystic ovarian appearance or morphology (PCOM) identified through ultrasound or anti-Müllerian hormone (AMH) levels. For women with irregular cycles and hyperandrogenism (approximately 70% of cases), ultrasound (practice point; PP) or AMH level testing (evidence-based recommendation; EBR) is not required for diagnosis. For women who only have either irregular menstrual cycles or hyperandrogenism, pelvic ultrasound or the newly added AMH level testing (but not both), is needed for adult PCOS diagnosis (PP) (Supporting Information, figure 1).1-4,24,25 Biochemical testing for hyperandrogenism is only needed without clinical hyperandrogenism (PP). For adolescents, both hyperandrogenism and ovulatory dysfunction are necessary for diagnosis, with both pelvic ultrasound (PP) and AMH level testing (EBR) not recommended due to lack of specificity in the pubertal transition.¹⁻⁴

Although the absence of core diagnostic features makes initial PCOS diagnosis post-menopause difficult, retrospective diagnosis is possible based on clinical features and, together with a historical diagnosis, can be considered enduring (consensus recommendation; CR). Importantly, it is now recommended that individuals with PCOS be recognised as having increased cardiovascular disease risk factors, cardiovascular disease and potentially cardiovascular mortality (EBR). Potential increased cardiometabolic risk in first-degree family members including diabetes, metabolic syndrome and hypertension were also recognised (EBR for male family members, PP for female family members). High risks of early onset impaired fasting glucose, impaired glucose tolerance and type 2 diabetes in PCOS were reiterated (EBR), while high risks of obstructive sleep apnoea (EBR) and endometrial hyperplasia and cancer

(EBR) were noted. Evidence-based screening recommendations are outlined in Supporting Information, figure 2.¹⁻⁴ Metabolic features exist independent of, but are exacerbated by, excess weight (EBR).¹⁻⁴

New recommendations highlight significantly higher risks in pregnancy, independent of age and body mass index (BMI), including early miscarriage, excess gestational weight gain, gestational diabetes, hypertension in pregnancy, preeclampsia, small for gestational age babies, preterm delivery and increased incidence of caesarean delivery (EBR). Health professionals should ensure that PCOS status is identified preconception or early in antenatal care, and women with PCOS should be identified, screened and monitored before and during pregnancy for prevention and treatment (EBR). ¹⁻⁴

Adolescent perspective

The guideline used the World Health Organization definition of adolescence, which defines it to be the period between ten and 19 years, which coincides with physiological changes in puberty including menstrual irregularities, hyperandrogenism and PCOM. These physiological changes overlap with adult PCOS diagnostic criteria, thus affecting diagnostic accuracy. 9,26,27 Although delayed diagnosis is commonly reported in adults, many adults also note a missed diagnosis in adolescence. The 2018 and 2023 international guidelines updated the Rotterdam consensus diagnostic criteria to evidence-based guideline criteria. These include recommendations to avoid using nonspecific features common in adolescence (defining PCOM by ultrasound [PP] or by AMH level [EBR]), to promote accurate diagnosis during this life stage and more clearly defining each diagnostic component¹⁻⁴ (Supporting Information, figure 1). Recognising the risk of underdiagnosis, the guideline also recommends identification of individuals with only one diagnostic criterion (hyperandrogenism or irregular cycles) as being "at risk of PCOS" and requiring follow-up (PP).¹⁻⁴ Adolescents with one criterion have greater weight gain, more metabolic and hyperandrogenic features than healthy adolescents, but less than individuals meeting both criteria, warranting reassessment (PP).

Timely diagnosis allows for identification and prevention in individuals who are at high risk of long term complications, before potential long term use of contraception, which can mask PCOS symptoms. ^{26,28} In adolescents "at risk" or diagnosed with PCOS, the guideline recommends combined oral contraceptive pill (COCP) alone or metformin alone (EBR). Evidence in adolescents with PCOS is relatively scarce with limited research to date. ²⁸ Notably, the prevalence of depressive symptoms and depression in adolescents with PCOS is high (EBR), yet management is often suboptimal with dissatisfaction reported in education, information and emotional support. ²⁷

Psychological health and wellbeing

All health professionals should be aware that PCOS carries increased risks of negative psychosocial outcomes and mental health conditions, including depression, anxiety, eating disorders, disordered eating, body image distress, low selfesteem and problems with feminine identity (EBR). These affect the quality of life (EBR) and likely the capacity to engage in PCOS-related lifestyle interventions and self-management (PP). Mental health guidelines rarely recognise PCOS as being associated with psychological conditions. Despite this, most people with PCOS report that these outcomes are underrecognised, with limited emotional support and counselling

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highlighting a need for increased awareness and reduced stigma regarding mental health symptoms (CR).¹⁻⁴ Treatment of other clinical features (eg, acne or hirsutism) can improve quality of life (PP) and, alongside psychological support (CR), needs to be prioritised.⁶

The guideline recommends that depression and anxiety are routinely screened for in PCOS (EBR), given the high prevalence.¹⁻⁴ Screening for depression and anxiety is common practice in Australia, particularly in the Better Access Initiative. Commonly used tools include the Depression, Anxiety Stress Scale³¹ and the Kessler Psychological Distress Scale.³² The Better Access Initiative facilitates up to ten individual and ten group Medicare-rebated sessions for mental health conditions. The guideline recommends that eating disorders and disordered eating are considered, regardless of weight, especially in the context of weight management and lifestyle interventions (EBR).¹⁻⁴ Although routine screening is not recommended, an assessment should be completed when eating disorders or disordered eating are suspected, 1-4 with the Eating Disorders Examination Questionnaire³³ commonly used in Australia, particularly in eating disorder treatment and management plans (PP). Individuals with mild to moderate eating disorders may be eligible for ten Better Access sessions (up to ten individual and up to ten group sessions per year), individuals with severe eating disorders may be eligible for up to 40 evidence-based psychological sessions, and up to 20 dietetic sessions annually. The guideline does not recommend routine screening, but does recommend that patients with body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction be offered evidence-based treatments (eg, cognitive behavioural therapy) where appropriate (CR). Individualised approaches focusing on personal priorities are recommended. 1-4

The guideline recommends psychological therapy be considered first-line (CR), and that women with depression, anxiety or eating disorders should be offered evidence-based psychological therapy, 34-38 as per general population guidelines and patient preferences (CR). Mental health interventions can be effectively delivered via multiple modalities including face-to-face, telephone, videoconference and online, including guided self-help interventions. Numerous high quality, Australian mental health support resources are available, including e-Mental Health in Practice, Head to Health, Black Dog Institute, Beyond Blue, Butterfly Foundation, Centre for Clinical Interventions, and This Way Up.

Models of care, quality information provision and shared decision making

Consumer input highlighted the critical need for the provision of high quality information (EBR) and for established interdisciplinary and patient-centred PCOS models of care with acknowledgement of unique experiences, concerns and goals (CR), 6,39 and adaptation for cultural and health care system factors. Health care professionals need to shift from traditional decision makers to empowering shared decision making and self-management (EBR). The models of care must build on evidence-based practice and necessitates multidisciplinary collaboration (CR). 40,41 In Australia, there are few dedicated models of care, except for the Victorian PCOS service, which aligns with guidelines and improves patient experience.⁴¹ The Victorian Government has recognised the need and is expanding services, whereas most other states and territories remain underserved. Enhanced health professional education, systematically embedded at all levels of health professional training, is recommended to address PCOS knowledge gaps (CR). Recommendations also target research and policy sectors to advance knowledge and improve care and health outcomes. Provision of comprehensive and accurate information is paramount for shared, informed decision making, 42 and to enhance knowledge and self-management. 42 Health care professionals have a vital role in engaging in open and respectful communication and providing guidance and support in individualised person-centred care.

Lifestyle management

Higher weight gain and higher weight are common features of PCOS with a two-fold higher risk of having overweight, obesity or central obesity.⁴³ Adverse lifestyle factors (higher energy intake, nutrition with high glycaemic index, increased sitting time and lower physical activity) have greater impact in PCOS, compared with controls.44 Lifestyle management should be recommended to all individuals with PCOS (EBR) and encompass both prevention of weight gain, and support for individuals with overweight or obesity (CR). Healthy lifestyle behaviours encompassing healthy eating and physical activity should be recommended to optimise general and metabolic health, and improve quality of life (CR), 1-4 noting benefits even without weight loss (PP). Within lifestyle interventions, behavioural strategies may increase engagement (PP).¹⁻⁴ Importantly, for dietary and exercise components, there is no one superior approach (EBR)⁴⁵ with practice guided by general population guidelines 46,47 and individual preferences and goals (CR), and referral to allied health professionals where required (PP).¹⁻⁴ Other healthy eating patterns recommended in national and international evidence-based guidelines for healthy eating, diabetes or cardiovascular disease prevention or management include the Mediterranean diet and the Dietary Approaches to stop Hypertension (DASH) diet. 48 Misinformation on fad diets should also be refuted and evidence-based information provided.

Co-developed, realistic and tailored lifestyle goals are key (PP), acknowledging that weight stigma and negative biopsychosocial impacts are common in PCOS (PP). Weight-neutral care could be considered where warranted or preferred with further research needed (PP). Health care professionals and policy makers need to recognise that the primary drivers of excess weight sit at a policy, environmental and social level, with 70% of Australians above healthy weight. This surpasses isolated individual behavioural lifestyle change and mandates broader population level strategies.

Management of non-fertility features

Medications for PCOS are generally off-label, or prescribed for an indication or patient group not specified in approved product information by the regulatory body, despite evidence of efficacy. This is unavoidable and common, usually due to lack of industry funded submissions to regulatory bodies, which are less likely with off-patent medications used in PCOS. COCPs are recommended in adults with PCOS or adolescents with or at risk of PCOS, for irregular cycles or hirsutism (EBR). 1-4,50 Lowdose preparations are recommended ($\leq 30\,\mu\mathrm{g}$ of oestradiol) for treating hirsutism in adults, with limited additional benefit with cyproterone acetate containing agents, which are second-line treatments, due to side effects (EBR). COCP use should align with general population guidelines and balance efficacy, metabolic risk, side effects, cost and availability (EBR). Mechanical laser and light therapies should be considered for

reducing hirsutism and for related depression, anxiety and quality of life in PCOS (EBR), ideally delivered by experienced practitioners (CR). In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy (EBR). 1-4,54

Metformin should be considered in adults with PCOS and a BMI $\geq 25\,\mathrm{kg/m^2}$ for anthropometric and metabolic outcomes including insulin resistance, and glucose and lipid profiles (EBR).⁵⁵ Metformin can be considered for irregular cycles where the COCP is contraindicated (PP) or in adolescents (EBR).^{52,55} Metformin should be considered over inositol for hirsutism and central adiposity, noting increased side effects with metformin (EBR). Inositol (in any form) may be considered in PCOS based on individual preferences and values, given limited harm, potential for reduced biochemical hyperandrogenism and metabolic measures, yet with limited evidence for clinical ovulation, hirsutism or weight benefits (EBR).

There is limited research on anti-obesity medications in PCOS. However, there is evidence in the general population allowing use with active lifestyle for weight management in adults with PCOS, as per population guidelines (CR), ensuring effective contraception given limited pregnancy safety data (PP).¹⁻⁴ In Australia, regulatory status is evolving but currently Pharmaceutical Benefits Scheme reimbursement of newer agents is limited to diabetes management and access can be challenging. Bariatric surgery can be considered for women with PCOS for weight loss, hypertension, diabetes prevention and treatment, irregular cycles and pregnancy rates, informed by population guidelines (CR).⁵⁶ Fertility can return soon after surgery, and pregnancy is not recommended until weight stability, requiring interim contraception (CR). Access and out-of-pocket costs are ongoing considerations. Finally, research into these interventions in PCOS was prioritised within the guidelines and the research priorities map. 1-4

Screening, diagnostic assessment and management of infertility

Women with PCOS should be reassured that pregnancy will often be successfully achieved either naturally or with oral ovulation induction (PP), especially with early PCOS diagnosis and a focus on prevention. Fertility treatment in PCOS should be guided by the fertility treatment algorithm (PP) (Supporting Information, figure 3).¹⁻⁴ Prenatal vitamin supplementation should be started (PP) (including folate, which needs to be given at a higher dose in individuals with a BMI $> 30 \text{ kg/m}^2$) and routine preconception care instituted (CR), to optimise comorbid conditions such as diabetes and high blood pressure (PP). Women should be counselled on the adverse impact of excess weight on fertility, miscarriage and live birth rates (EBR), while avoiding weight stigma and considering cultural, social and environmental determinants of health (PP). Blood pressure, smoking, alcohol, diet, nutritional status, exercise, sleep, mental, emotional and sexual health should be considered and optimised (CR).¹⁻⁴

The risks, benefits, costs, timing and techniques of tubal patency testing before starting ovulation induction should be considered on an individual basis in the presence of anovulation with normal semen analysis (CR). Use of ovulation induction agents is off-label in Australia but allowed, and health care professionals need to inform women and discuss evidence, concerns and side effects (PP). Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS with no other infertility factors

(EBR). Other less effective ovulation induction agents, such as metformin, clomiphene citrate and combinations thereof, may be considered following explanation of benefits, risks, efficacy and costs (EBR). $^{1-4}$

Either gonadotrophins (low dose) or laparoscopic ovarian surgery could be second-line treatment options for anovulatory and infertile PCOS, with clomiphene citrate resistance and no other infertility factors (EBR), following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins, and considering expertise, monitoring, risks and costs. In the absence of an absolute indication for in vitro fertilisation or intracytoplasmic sperm injection, in vitro fertilisation could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies fail (CR). Alternatively, in vitro maturation can be considered with adequate expertise, acknowledging less effectiveness for cumulative live birth rate but better potential safety for ovarian hyperstimulation syndrome (EBR).¹⁻⁴ These recommendations are applicable to the Australian health care system, including pre-pregnancy care usually provided by general practitioners and secondary fertility care involving specialist referral.

Translation

Recommendations are supported by evidence-based, freely accessible co-designed resources for health professionals (algorithms, webinars, toolkits and training programs) and patients (ASKPCOS app reaching 196 countries and more than 60000 women is available at https://mchri.org.au/guidelines -resources/community/askpcos-app/; fact sheets [Supporting Information, figure 4], booklets and webinars, in multiple languages and available at https://mchri.org.au/guidelines-resou rces/community/pcos-resources/). Co-development of a best practice framework to guide models of care and of sophisticated digital tools are underway for interactive, shared decision making. Evaluation includes benchmarking models of care and ongoing assessment of the Australian Longitudinal Study of Women's Health data on diagnosis, screening and treatment aligned to guideline recommendations nationally. Translation is prioritised and funded and will include broad engagement with relevant stakeholders. This will include Indigenous Australians, with higher PCOS prevalence and more limited access to care in regional, rural and remote areas.

Conclusion

The 2023 guideline targets recommendations towards training organisations, policy makers, research funders, health professionals and individuals with PCOS. Overall, the guideline responds to limited education, inadequate research and models of care and takes a strong patient-centric approach to support women with PCOS and health professionals in Australia and globally. The guideline process has generated a research priorities map to guide future research and translation. The guideline also emphasises the need for a best practice framework for effective models of care and for greater medical and health professional undergraduate and postgraduate education, with work currently underway in this area. For individuals with PCOS, improved knowledge transfer and optimised shared decision making is important. We encourage all stakeholders to recognise this common, neglected condition and to implement evidence-based recommendations for improving diagnosis and care experiences and optimising health outcomes for the one in eight Australian women affected by PCOS.

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Supporting Information

Additional Supporting Information is included with the online version of this article.