

National Audit of Testing for the Peri/menopause on behalf of the National Audit Group

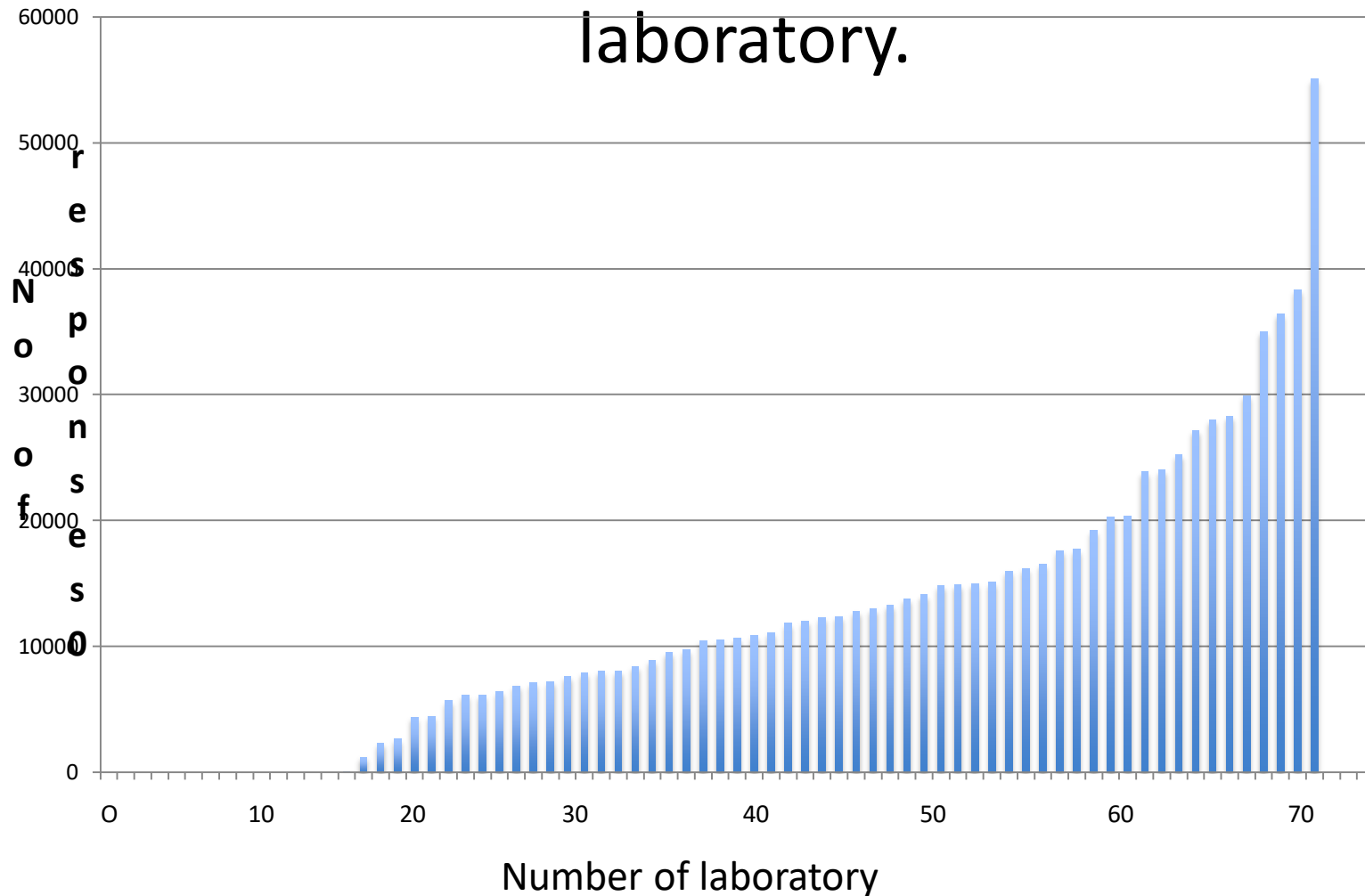
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and Theresa Teal, RHCH



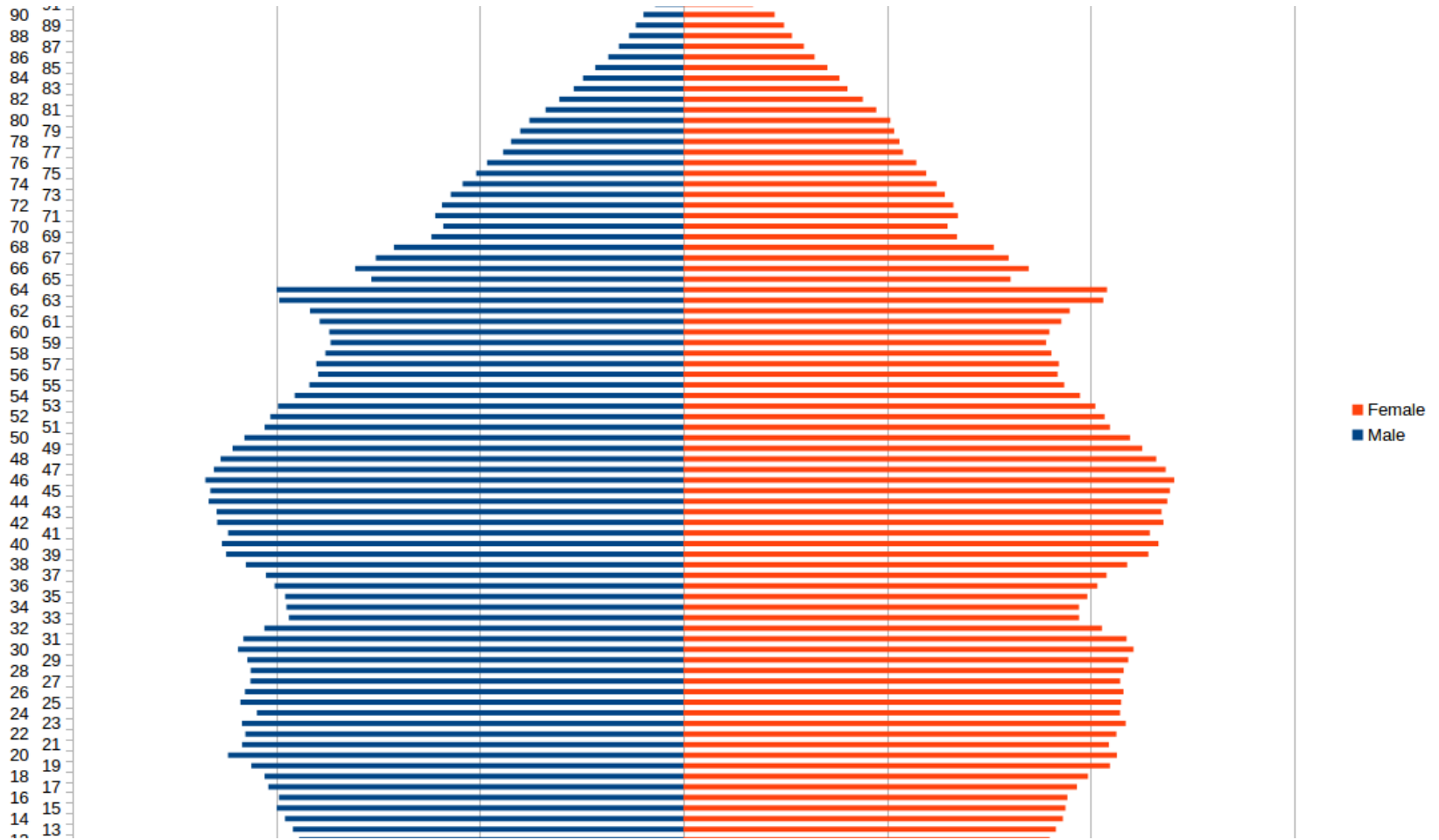
**The Association for
Clinical Biochemistry &
Laboratory Medicine**

Better Science, Better Testing, Better Care

Number of requests for female FSH, LH and gonadotrophins received per annum for in each laboratory.



Demography of the UK 2011 Census



Estimate of the number of women 45-54y tested for the ? Perimenopause/menopause at Southampton General.

- UHSFNT serves a population of 1 million for Primary Care
- The Census shows that men and women 45-54 years represented 13.8% of the total population
- There were equal numbers of men and women in the age band 45-54 years
- Therefore women 45-54 years = 6.9% of the population which is 69,000 women
- Total requests for ? menopause/perimenopause was for 2014 was 2012 after excluding legitimate tests (audit, Selina Lee) which means that approximately 2.9% of women were tested in that year.
- We estimate that if each women was tested once 29% of the women 45-54 y would be tested over a 10 year period-
- Some women are tested more than once so allowing for this reduces the figure to 23%.

National standards

- There are were no nationally agreed standards available for the purposes of this audit in January 2015.
- So draft guidelines formulated from:
 - Local guidelines, prepared with a local Consultant Endocrinologist
 - The Welsh guidelines
 - An algorithm prepared by Geoff Beckett et al (Edinburgh).

Audit

- Initiated in response to the current climate of cost effective and evidence based medicine.
- This audit will attempt to establish how gonadotrophin requests, made in response to queries about the menopause, are dealt with by laboratories.
- The way they are reported
- Consider whether practice is in line with the agreed standards (January 2015).

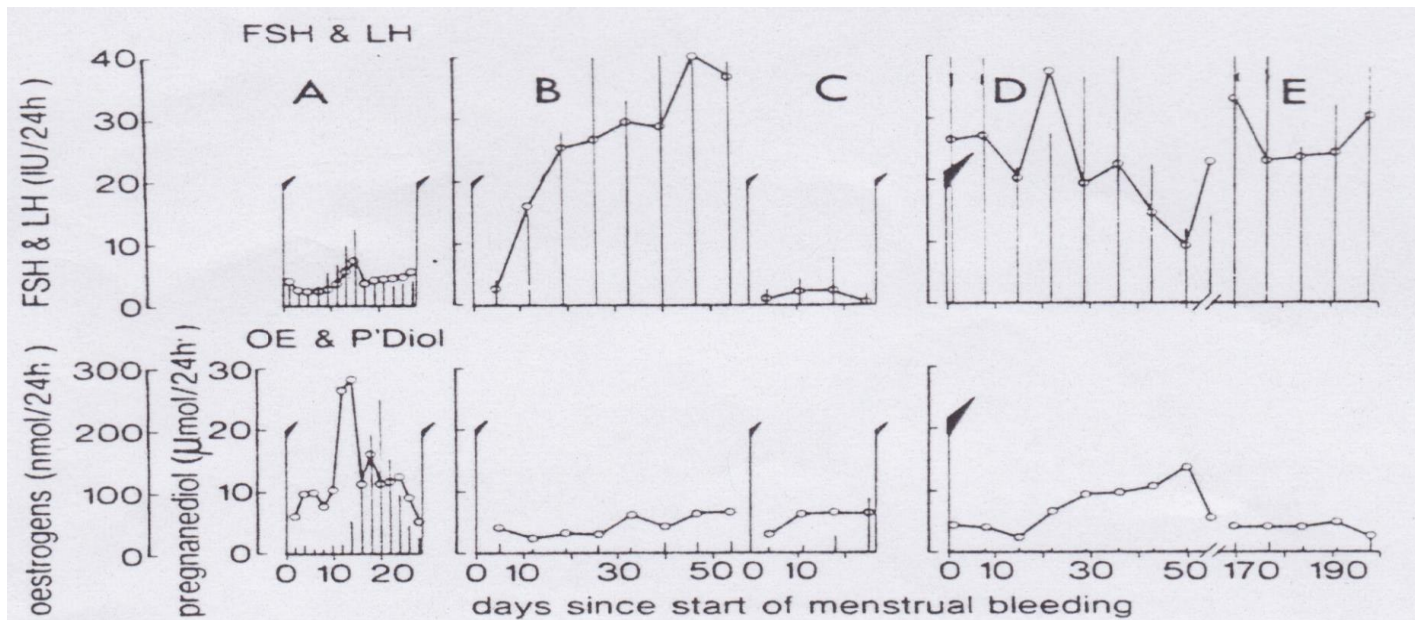
Standards for this audit

Standard 1) Plasma FSH can be difficult to interpret because levels may rise and then fall again into the reference range.

Standard 2) Normal biochemical values can be seen in patients who have begun the menopause transition with normal gonadotropins levels in up to 30% of cycles.

Metcalf 1988: Importantly stated as long as menstruation is regular in women over 40 years old they continue to ovulate.

Excretion of FSH (O-O) and LH (vertical bars) and oestrogen (o-o) and pregnanediol (vertical bars) during the menopause transition.



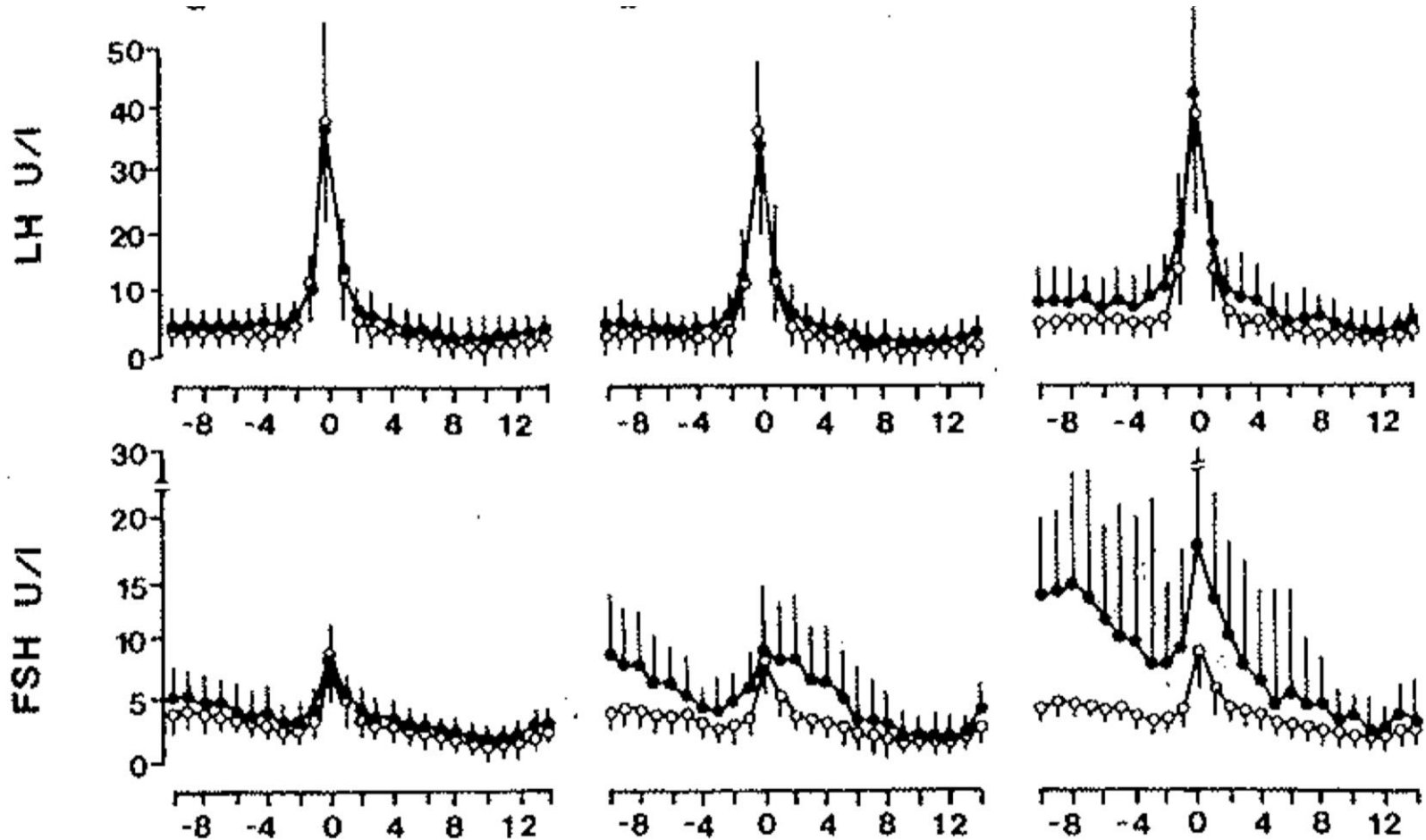
Metcalfe 1988

- Fertile cycles can occur right up to the time of the menopause.
- Importantly stated as long as menstruation is regular in women over 40 years old they continue to ovulate

Standard 3

If required, an FSH measurement is usually sufficient, providing due consideration to changes in the FSH reference range with age and those associated the mid-cycle peak

Comparison of the daily geometric mean concentrations of LH and FSH (with 67% confidence intervals) in women with normal cycles from Lee et al (1988)



41 women 24-35 y (o-o
vs women 36-40 (•-•)

41 women 24-35 y (o-o
vs women 41-45 (•-•)

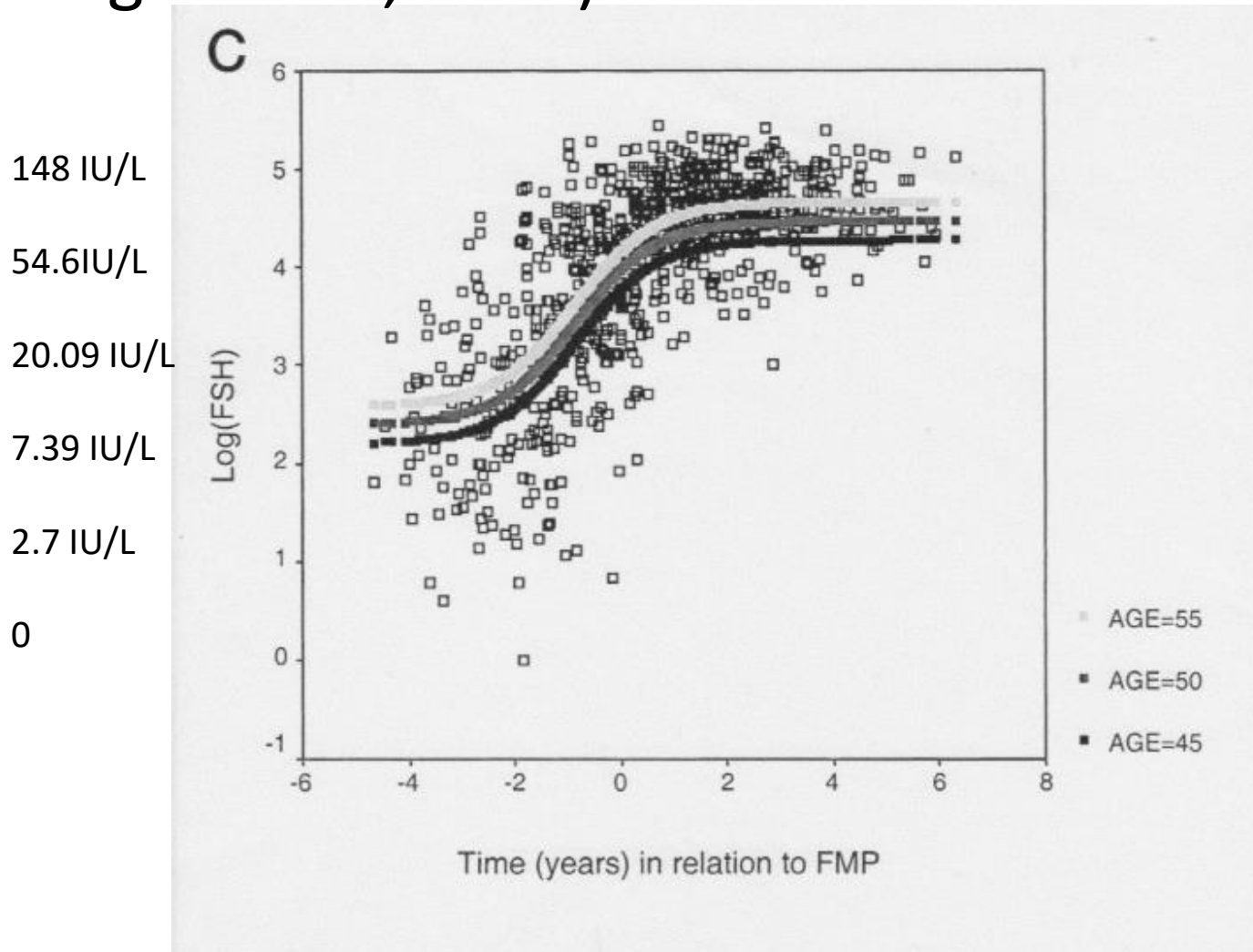
41 women 24-35 y (o-o
vs women 46-50 (•-•)

Standards continued

Standard 4) There are no biochemical parameters which guarantee the post-menopausal state.

Hormone measurements cannot be used as a guide as to when contraception is withdrawn.

Observed and fitted levels for mean log (FSH) across the menopausal transition, stratified by age (Berger et al , 1999).



Standards

- Standard 5) Gonadotrophin measurements are not recommended in women over 45 years with convincing history of the menopause.
- Standard 6) If FSH is to be measured in women who continue to have normal cycles then arrange for a sample to be taken on day 1-3 of the cycle as this improves discrimination.
- Standard 7) In younger women with suspected premature menopause or those who are post-hysterectomy, post-chemotherapy or post-radiotherapy a documented gonadotrophin profile is important for ongoing management.
- The menopause is reported to be advanced by 3-4 years post-hysterectomy and therefore annual gonadotrophins measurements are advised.

How do these standards fit in with other internationally agreed guidelines?

- In 1981 WHO, in a Scientific Group report, recognized the importance of clinical presentation when diagnosing the menopause and concluded that hormone measurements were unnecessary.
- British Menopause Society 2009
- American Association of Clinical Endocrinologists 2011
- International Menopause Society 2013
- The North American Menopause Society
- Nature Reviews 2015

FUGH



'I'm so much fitter now – it's all this running away from him'

Australian Menopause Society 2012

Symptom Score

- Severity of symptom is scored as follows:
- Score: Not present=0; Mild=1; Moderate=2; Severe=3.
- A score of 20-50 is common in symptomatic women.

Australian Menopause Society Symptom Score- severity of problem is scored as follows:

Score: None=0; Mild=1; Moderate=2; Severe=3. A score of 20-50 are common in symptomatic women.

Symptom	
Hot flashes	Joint pains
Light headed feelings	New facial hair
Headaches	Dry skin
Irritability	Crawling feelings under the skin
Depression	Less sexual feelings
Unloved feelings	Dry vagina
Anxiety	Uncomfortable intercourse
Sleeplessness	Urinary frequency.
Unusual tiredness	Backache

Endocrine Society Menopause Map 2012

<http://.hormone.org/MenopauseMap>

LET'S TALK ABOUT IT

Watch our new video

NETWORK FOR THE ENDOCRINE SOCIETY

MENU

HEALTH CARE PROFESSIONALS

WEB Health AWARDS™
winner: summer/fall 2014

Are you going through some changes?
Chances are you don't want to talk about them.
You're not alone.

Learn more about your personal journey with menopause.

Start your Journey

The Menopause Map™ will help you:

- Understand the stages of menopause
- Symptoms of menopause
- Treatment options for menopause

You don't have to suffer in silence any longer...
Let's Talk About It!

EN ESPAÑOL

Draft NICE June 2015

1. Diagnose the following without laboratory tests in otherwise healthy women aged over 45 years with menopausal symptoms:

Perimenopause based on vasomotor symptoms and irregular periods

Menopause in women who have not had a period for at least 12 months

Menopause based on symptoms in women without a uterus.

2. Take into account that it can be difficult to diagnose menopause in women taking sex steroids.

3. Do not use the following laboratory and imaging tests to diagnose perimenopause or menopause in women aged over 45 years:

Anti-Müllerian hormone

Inhibin A

Inhibin B

Oestradiol

Antral follicle count

Ovarian volume.

5. Consider using a FSH test to diagnose menopause only:

In women aged over 45 years with atypical symptoms

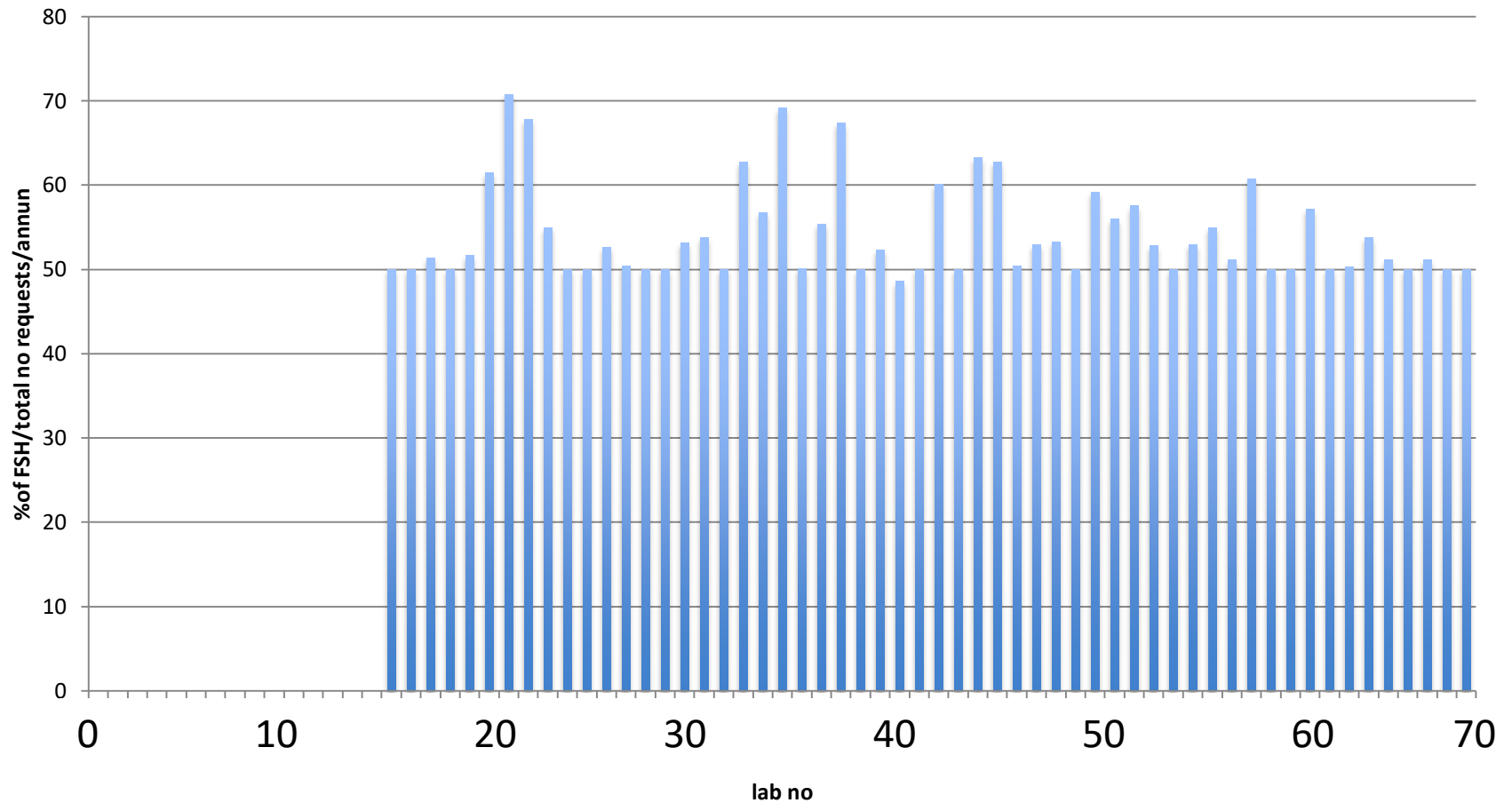
In women aged 40 to 45 years with menopausal symptoms, including a change in their menstrual cycle

In women aged under 40 years in whom menopause is suspected

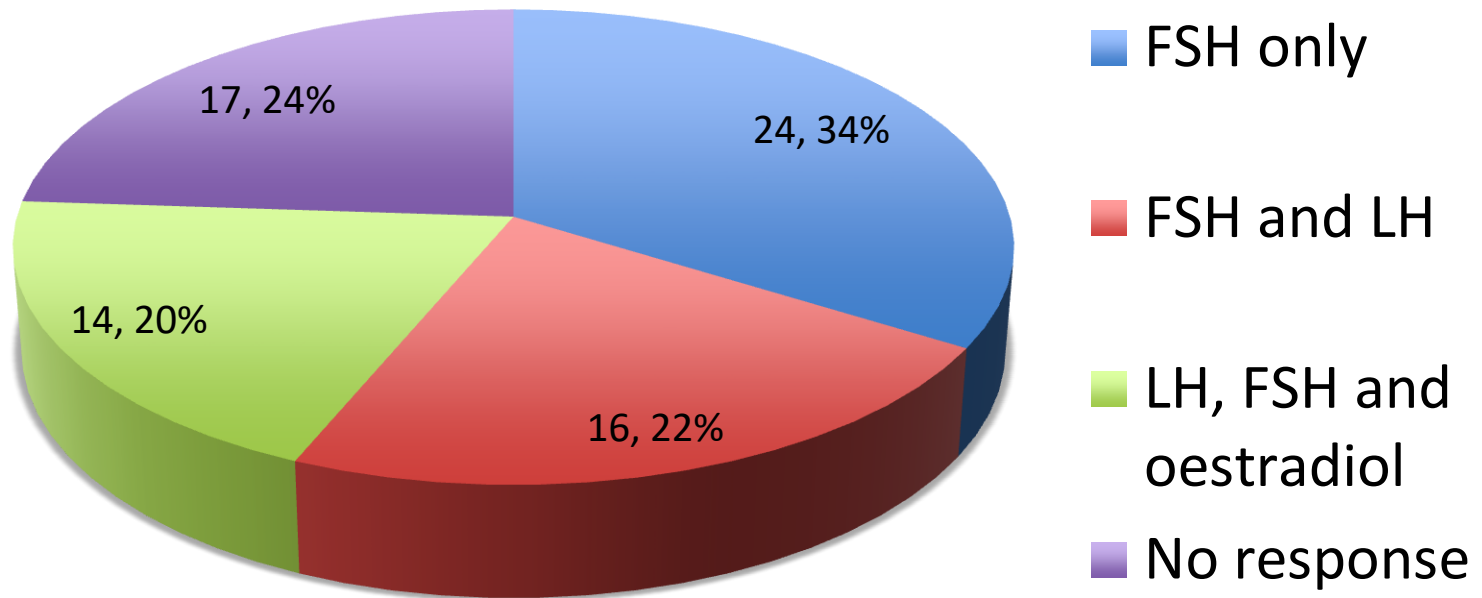
Premature ovarian insufficiency

- **11.1.8 Recommendations**
- **54. Take into account the woman's clinical history (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency.**
- **55. Diagnose premature ovarian insufficiency in women aged under 40 years based on:**
 - Menopausal symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) and elevated FSH levels on 2 blood samples taken 4–6 weeks apart.
- **56. Do not diagnose premature ovarian insufficiency on the basis of a single blood 1 test.**
- **57. Do not routinely use anti-Müllerian hormone testing to diagnose premature ovarian insufficiency.**
- **58. If there is doubt about the diagnosis of premature ovarian insufficiency, consider anti-Müllerian hormone testing after seeking specialist advice (see the NICE 6 guideline on fertility).**

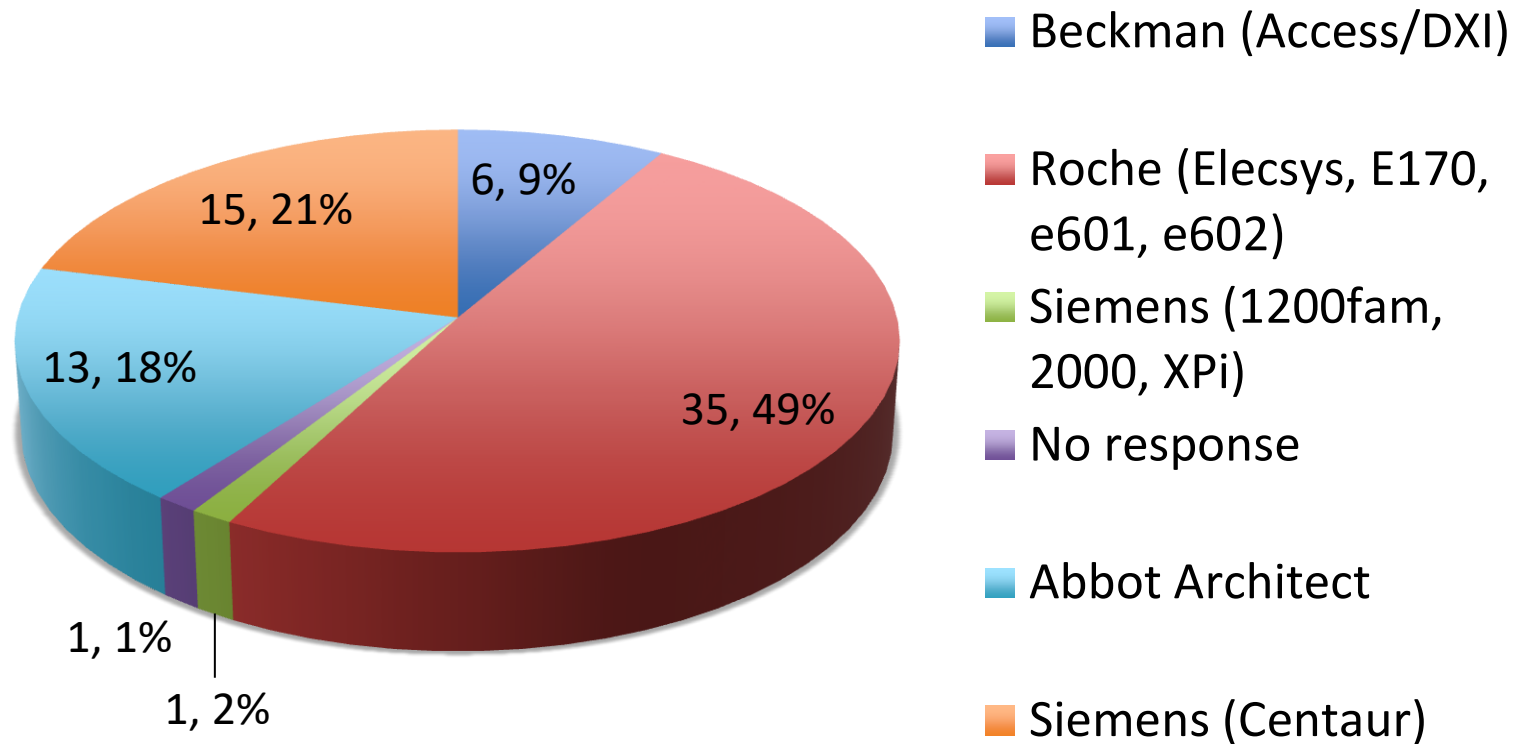
2) FSH only requests as a total of all gonadotrophin requests



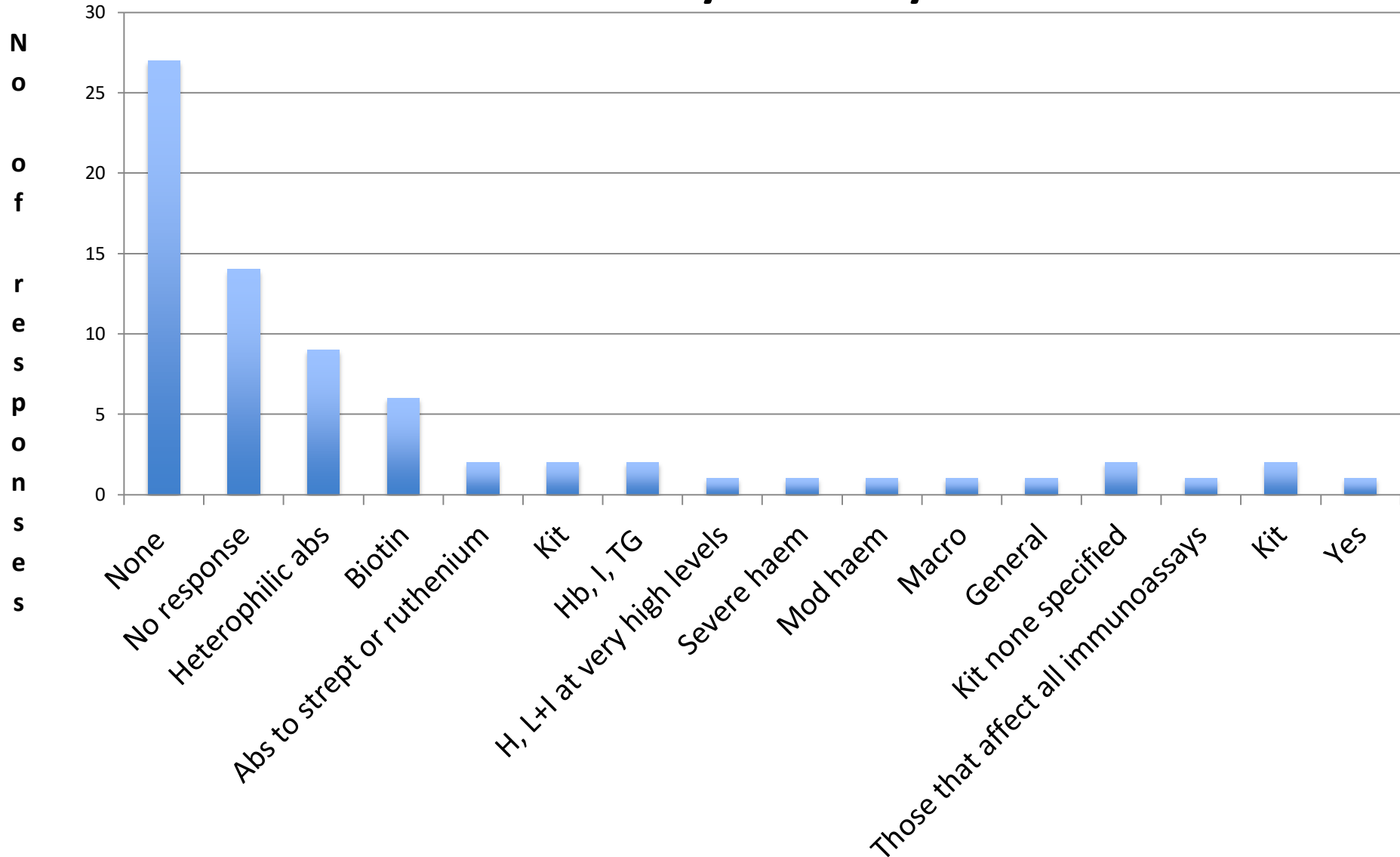
5) Which measurements do you offer for women who are “query menopausal”?



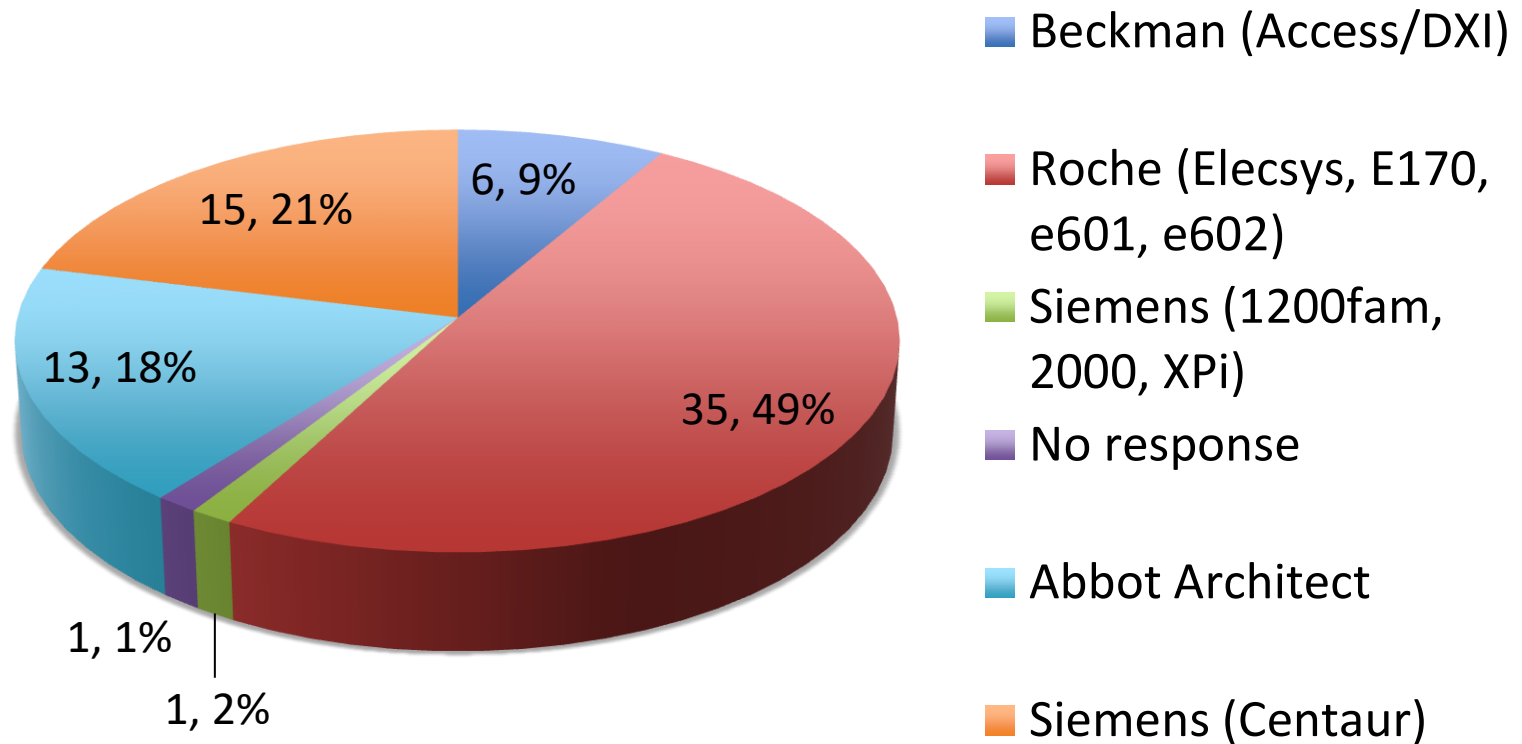
3) Which methods do you use to measure serum gonadotrophins?



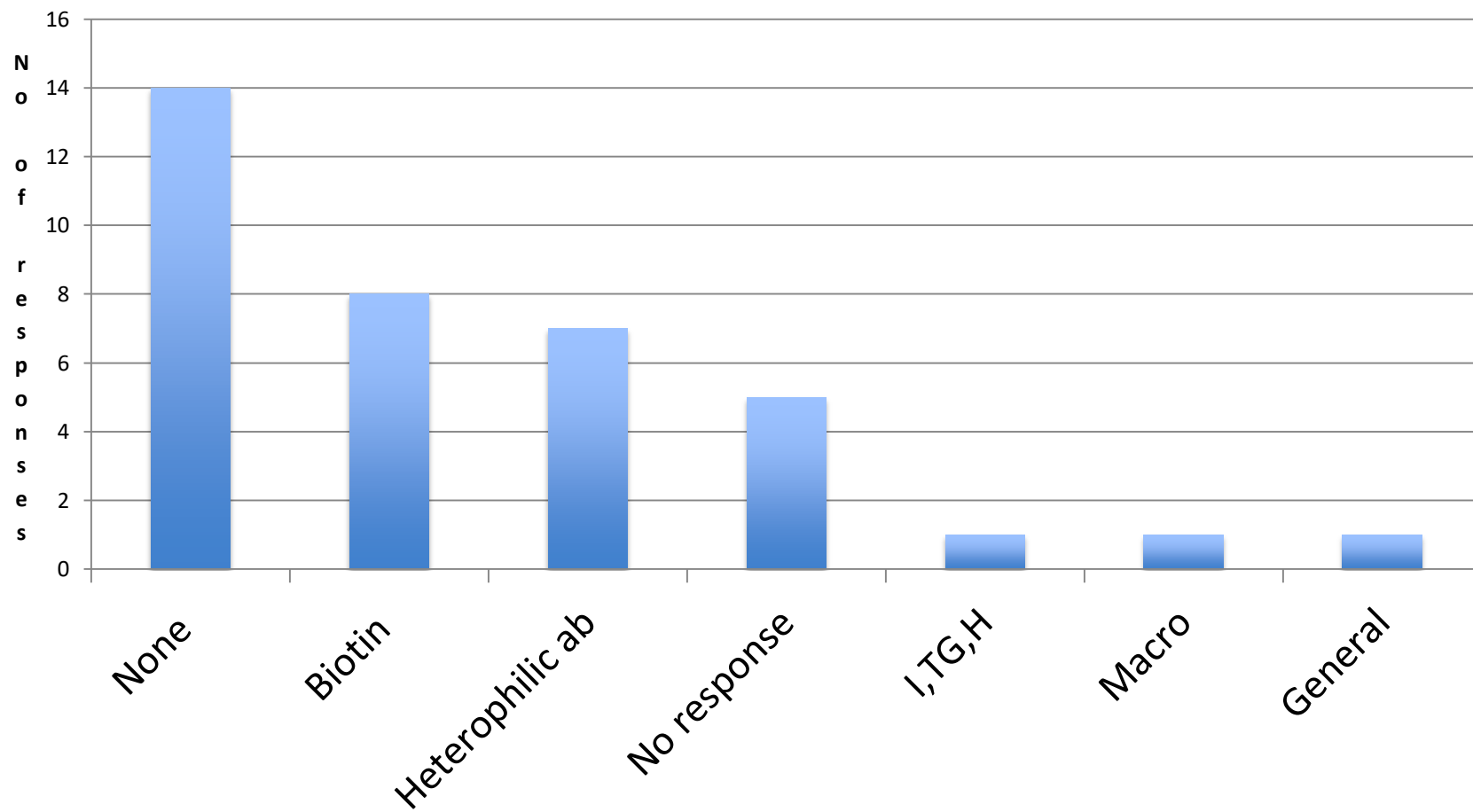
4) Are there any known interferences in the FSH assay that you run?



3) Which methods do you use to measure serum gonadotrophins?



Roche assays- known interferences in the FSH assay that you run



Interference or limitation

Analyte	Concentration	Interference	Limitation	Interference-limitation
Biotin	>5 mg/day			
None bilirubin	<1094 $\mu\text{mol/L}$			
None heamolysis	<10 g/L			
None lipeamia (Intalipid)	<19 g/L			
<u>Antibodies</u>				
Ab to ruthenium red				
Ab to Steptavidin				
Analyte specific antibodies (heterophile etc)				

Roche Assay Interference FSH

- Limitations-interferences:
- Samples should not be taken from patients receiving high doses biotin (i.e. >5mg/day)
- Unaffected by icterus (<1094 $\mu\text{mol/L}$)
haemolysis (Hb<10g/L) lipaemia
(intralipid<19g/L)
- No high dose Hook effect
- Rare cases interference due to extremely high titers of antibodies to analyte specific antibodies, streptavidin or ruthenium.

Abbot Architect Assay Interference

FSH

- Interferences: No interference Hb <10% at 5g/L, bilirubin <10% at 2g/L, TG <10% at 30g/L, protein <10% at 20g/L
- Limitations: Specimens from patients who have received preparations of mouse monoclonals may contain human anti-mouse antibodies
- Heterophilic antibodies can react with reagent immunoglobulins interfering with in vitro immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference.

Siemens Centaur Assay interference

FSH

Interferences

Insignificant effect of:

- Hb 1.5g/L
- Lipaemia 10g/L
- Bilirubin 200mg/
- Limitations

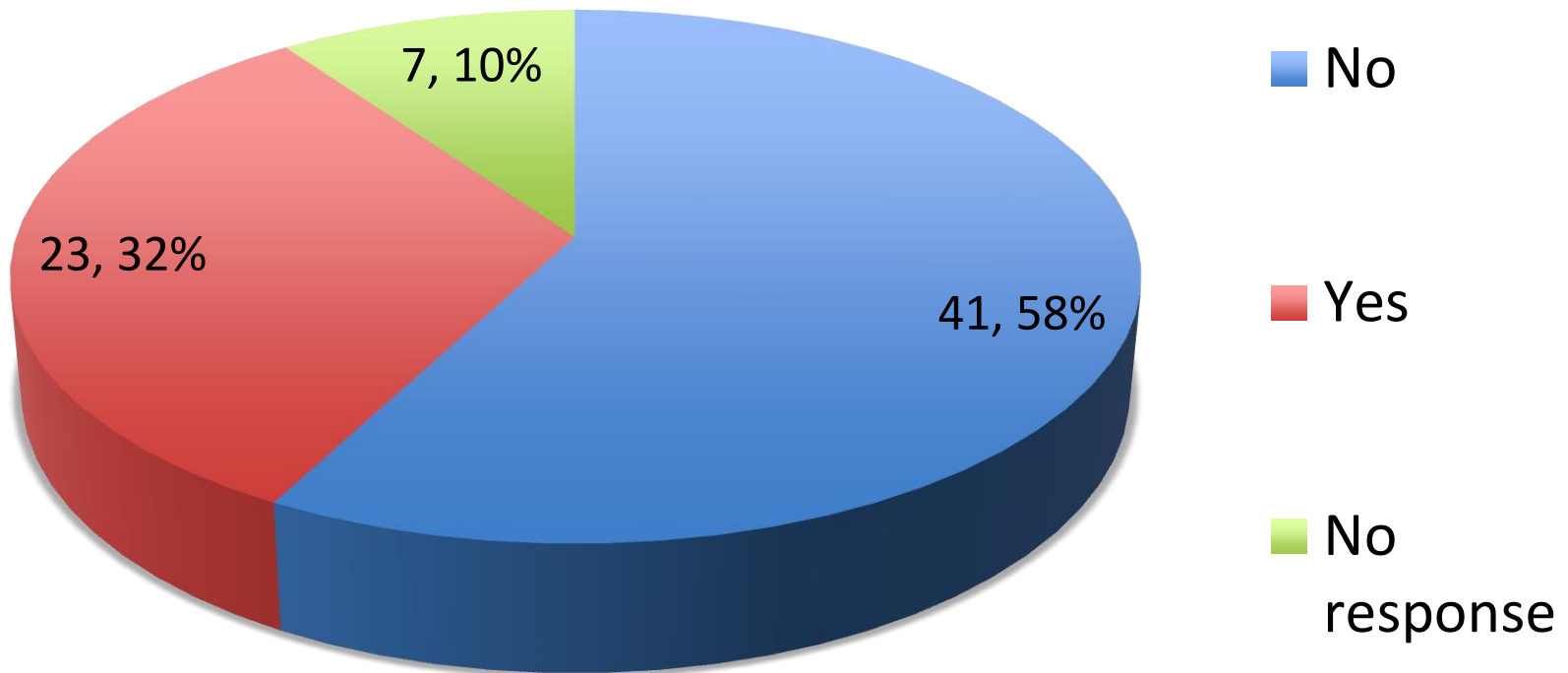
Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with in-vitro immunoassays. Patients routinely exposed to animals or to animal serum products are prone to this interference.

Beckman Assay interference FSH

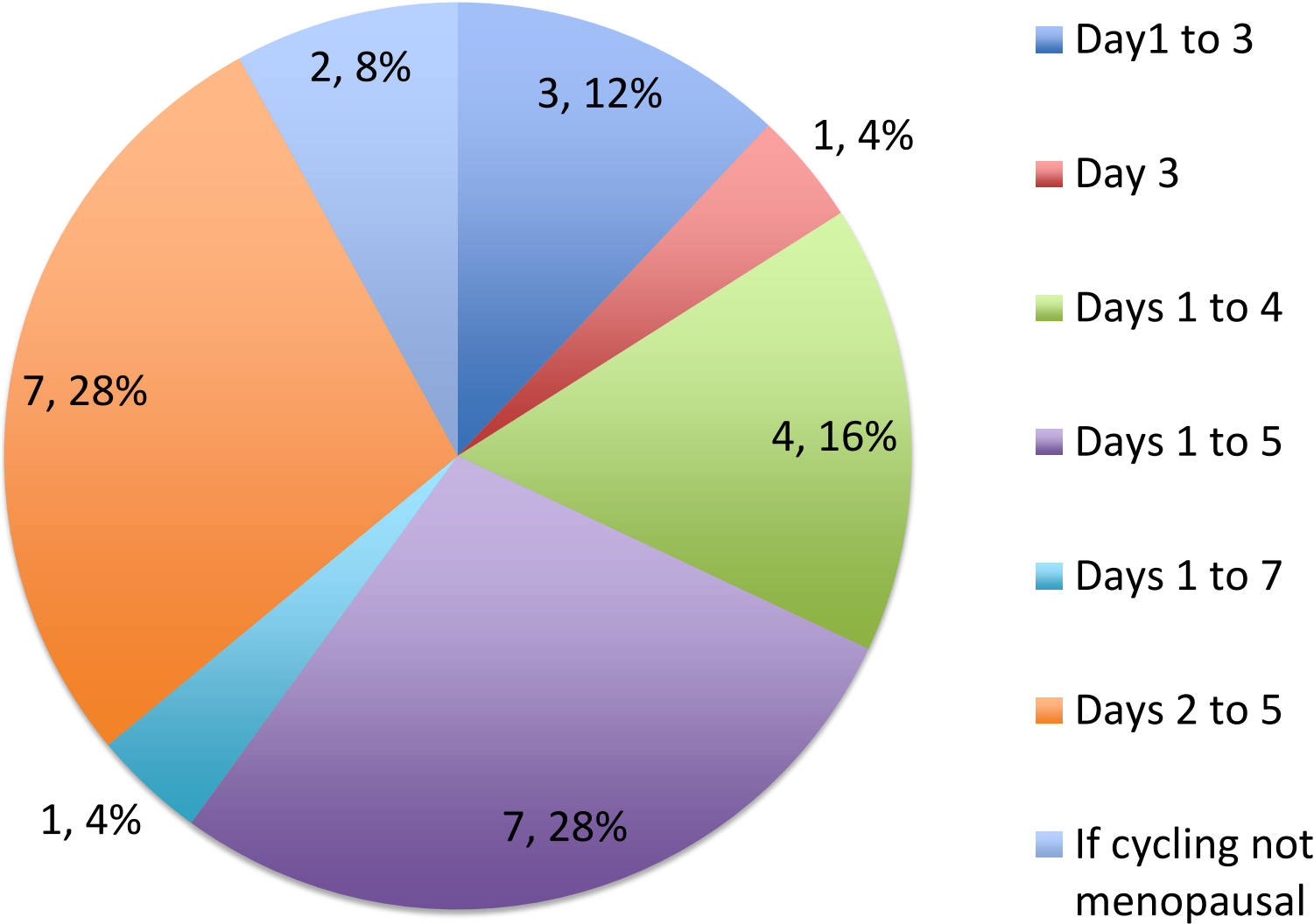
- Analytical Specificity and interferences: No effect of bilirubin <100mg/L (171umol/L), lipaemic <18g/L TG, Hb <10g/L.
- No significant cross reactivity hCG, hLH and hTSH
- Limitations of the Procedure: For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample.
- Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic utilizing immunoglobulins or immunoglobulin fragments may produce antibodies that interfere with immunoassays.

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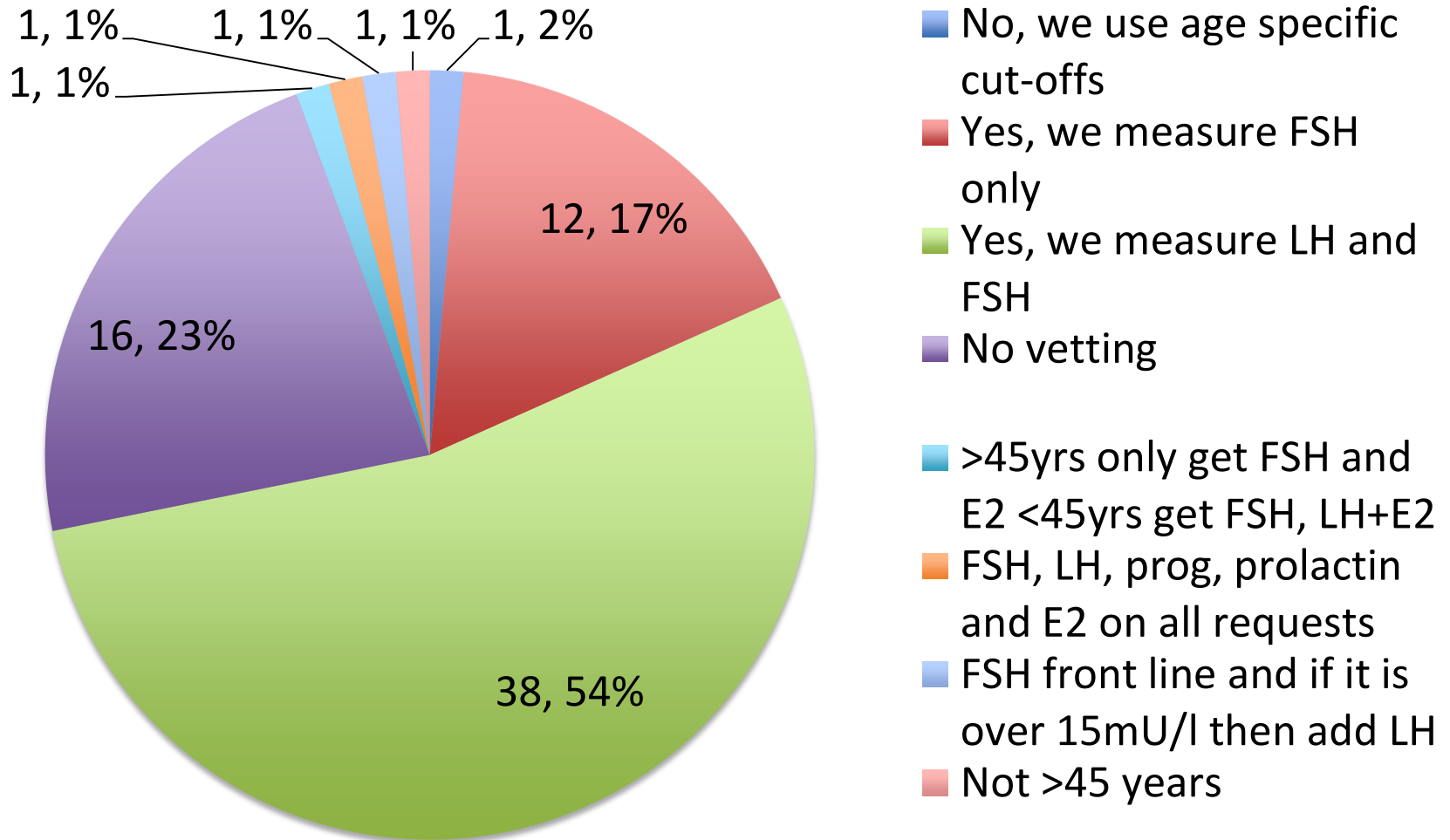
6) Do you recommend that samples from patients where the menopause is being queried are taken at a particular stage in the cycle and if so, on what day(s)?



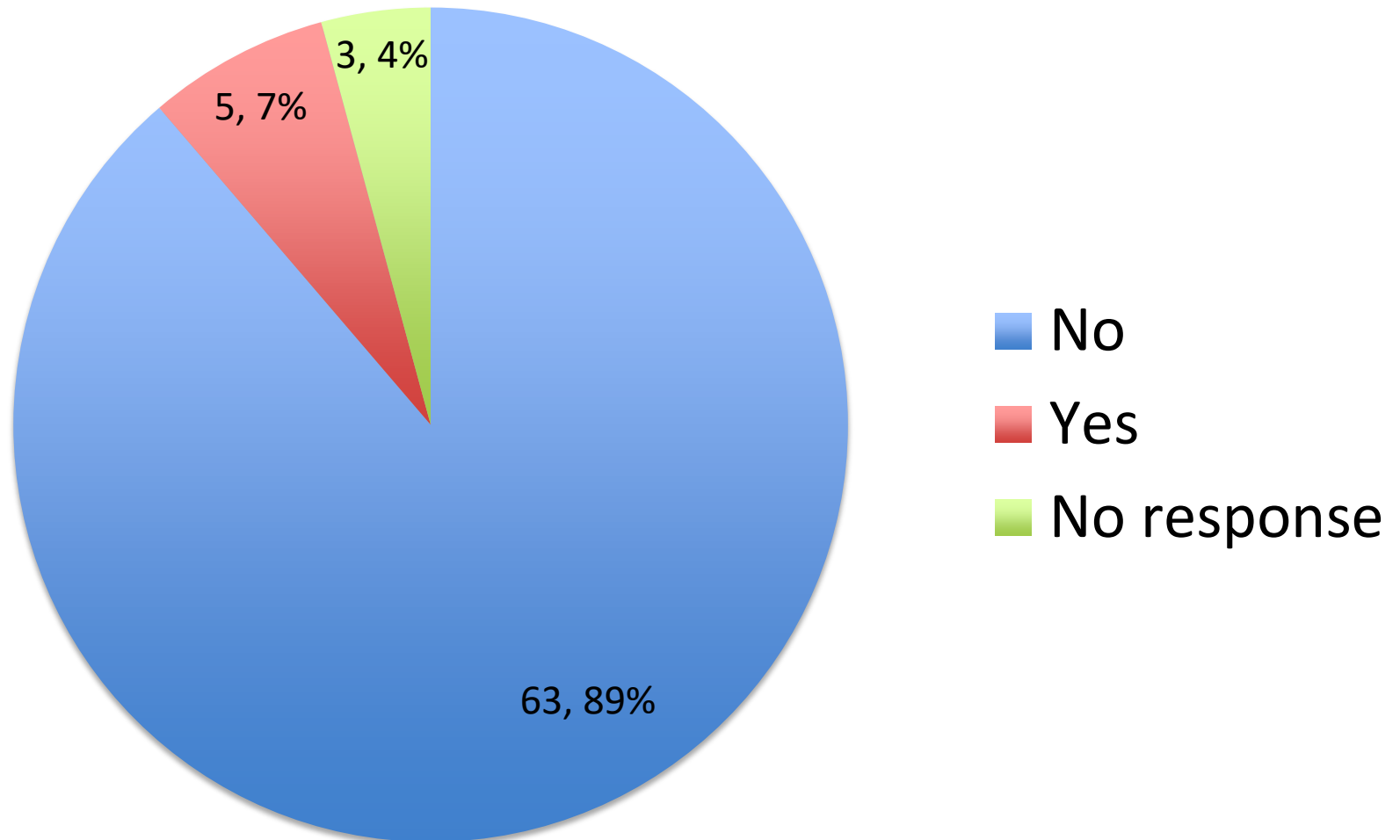
6b) What day do you recommend that samples from patients where the menopause is being queried are taken, please state day(s) of cycle



7) Do you analyse all requests for gonadotrophins where the perimenopause is being investigated?



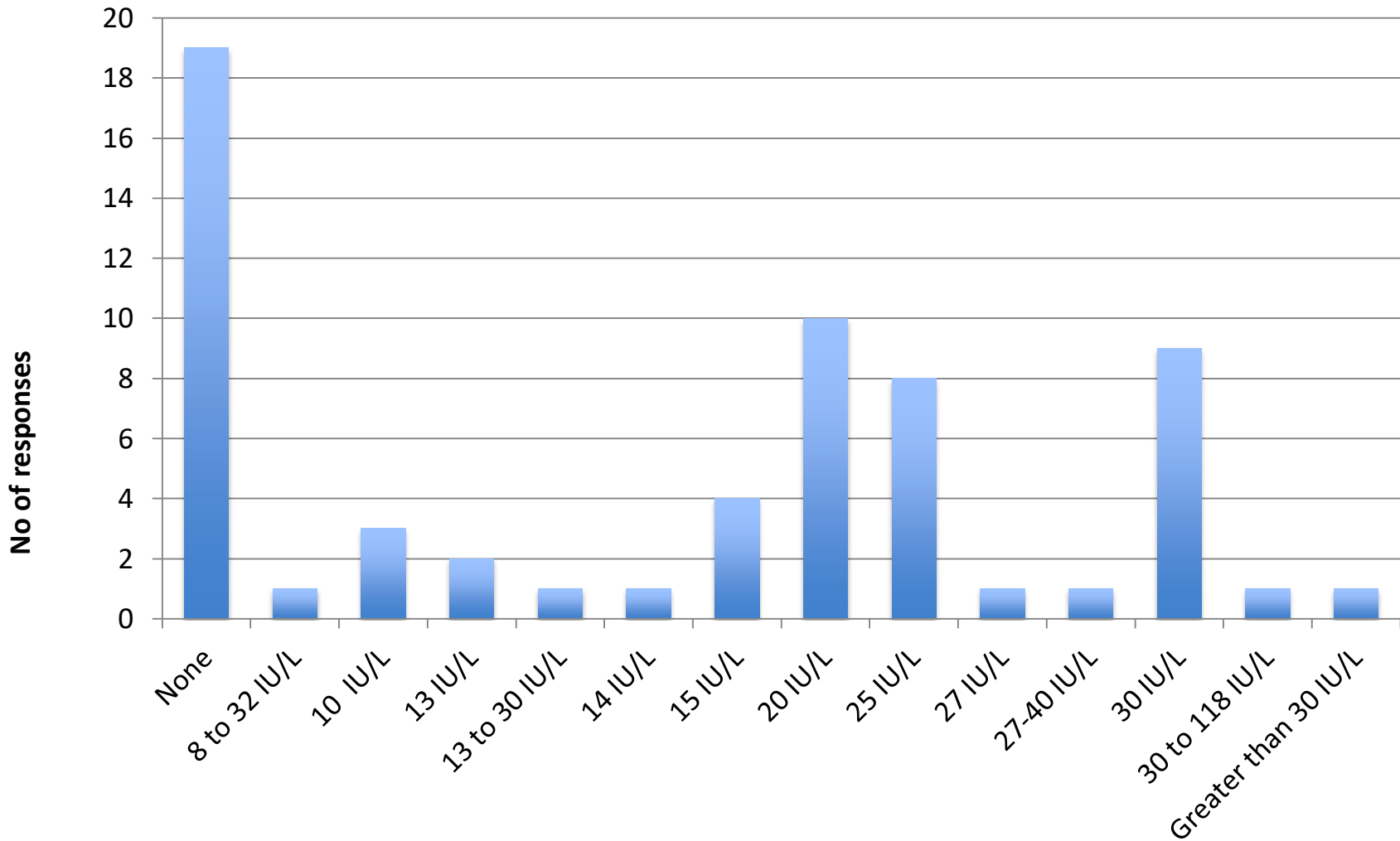
8) Do you have rules-based order communications for gonadotrophin requests for samples where evidence is being sought for the perimenopause?



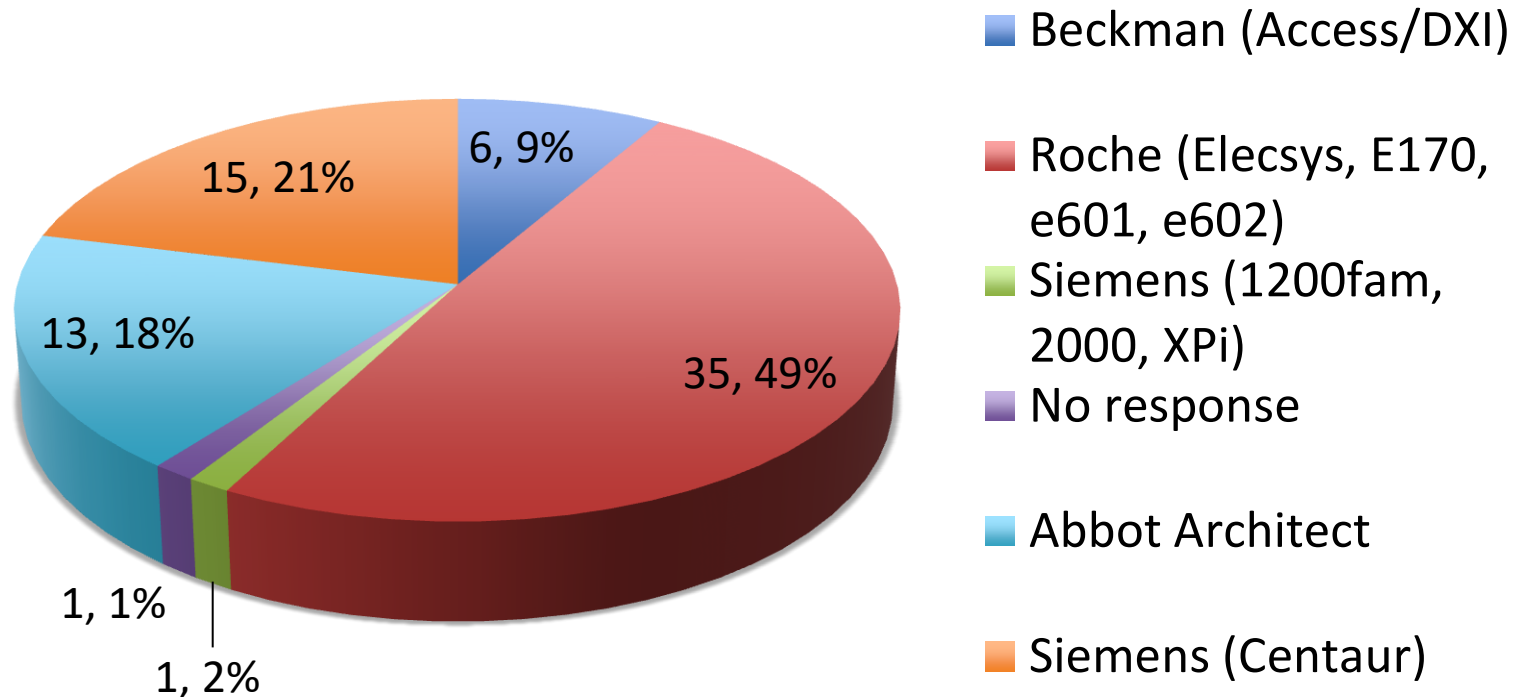
8 a) Rules-based order communications for gonadotrophin requests where evidence is being sought for the perimenopause? (3/5 comments shown)

- For all Gn requests a test is requested which goes to clinical approval – the duty biochemist adds tests as appropriate.
- For females aged 15-50 years the requestor is prompted to enter the date of the LMP and then FSH is requested as the front line test. If this is over 15 IU/L an LH is added automatically
- Menopause profile consists of frontline FSH, LH added if FSH 13-40 IU/L

9) What cut-off value for FSH do you use to advise if a woman has entered the perimenopause?



3) Which method do you use to measure serum gonadotrophins?

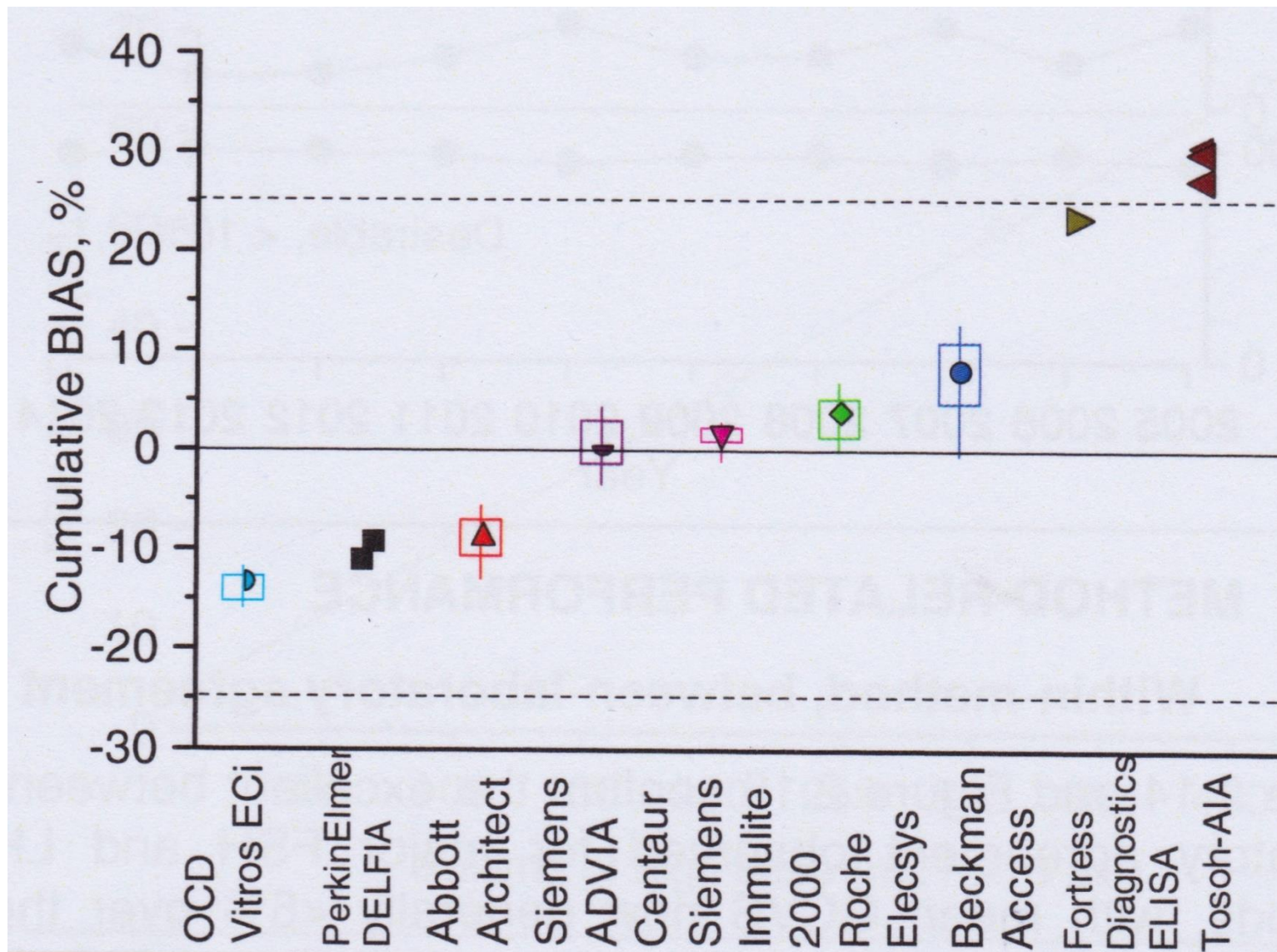


Manufacturers reference ranges

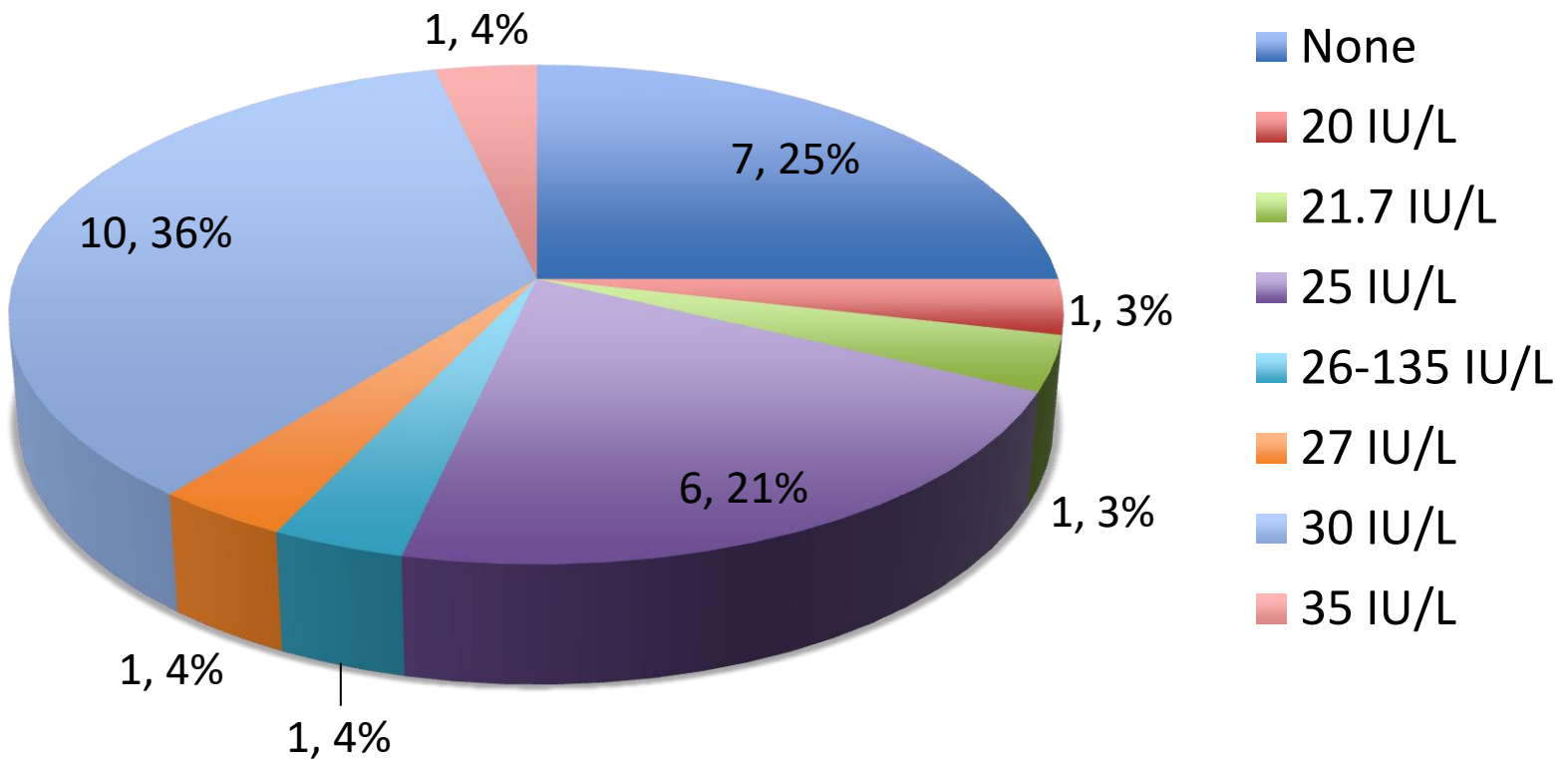
- Architect post menopausal 0026.72-133.41 IU/L
- Beckman post menopausal 16.74-113.59 IU/L
- Roche post menopausal (5th-95th centile) 25.8-134.6 IU/L
- Siemens Centaur post menopausal 23.0-116.3 IU/L

UK-NEQAS data 2014 report courtesy of Sturgeon

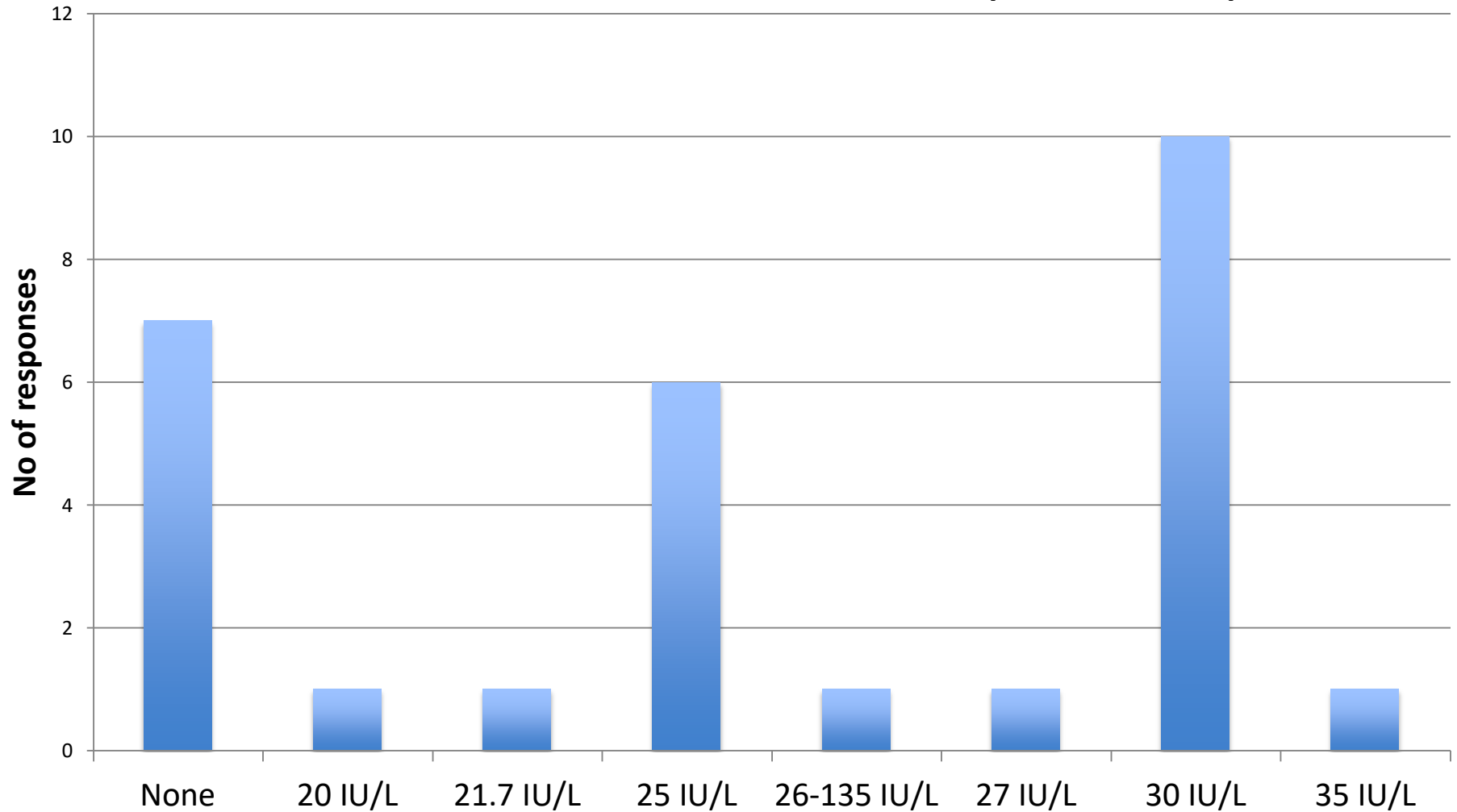
FSH Cumulative bias for all methods-mean, interquartile range (box) and 10th-90th centiles (whiskers), individual labs for minor methods



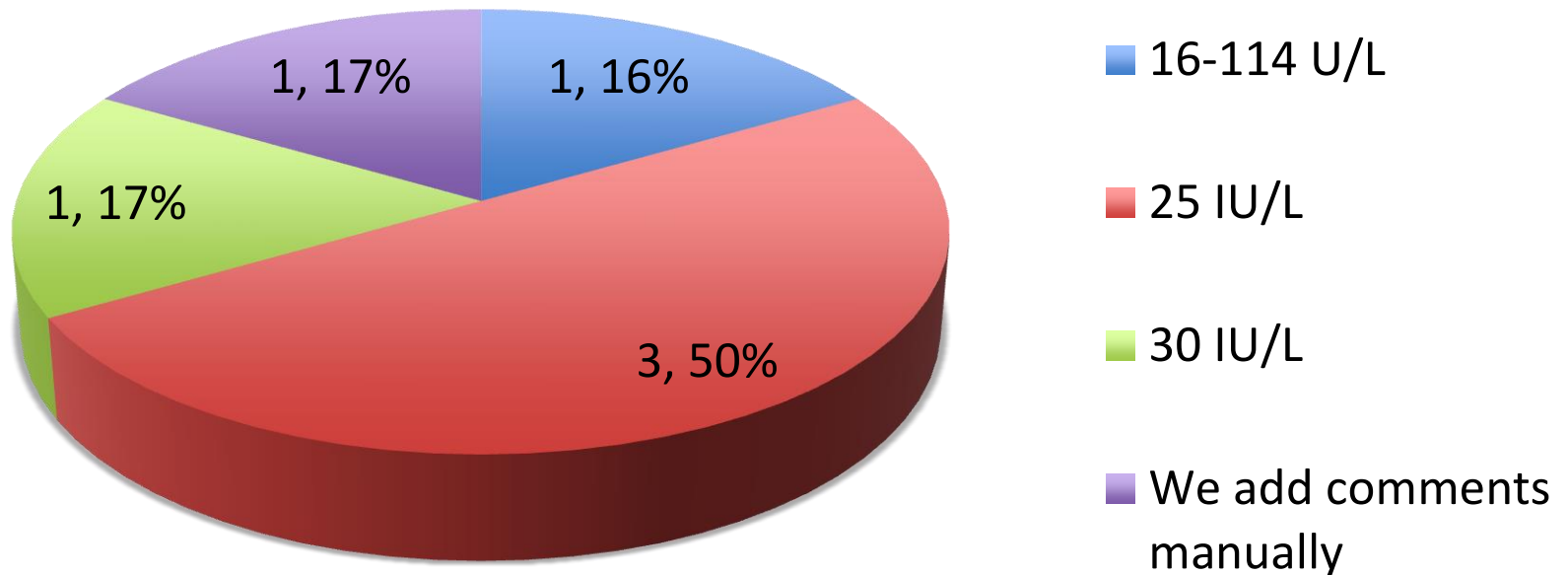
9 (a) Roche users: What cut-off value for FSH do you use to advise if a woman has entered the perimenopause?



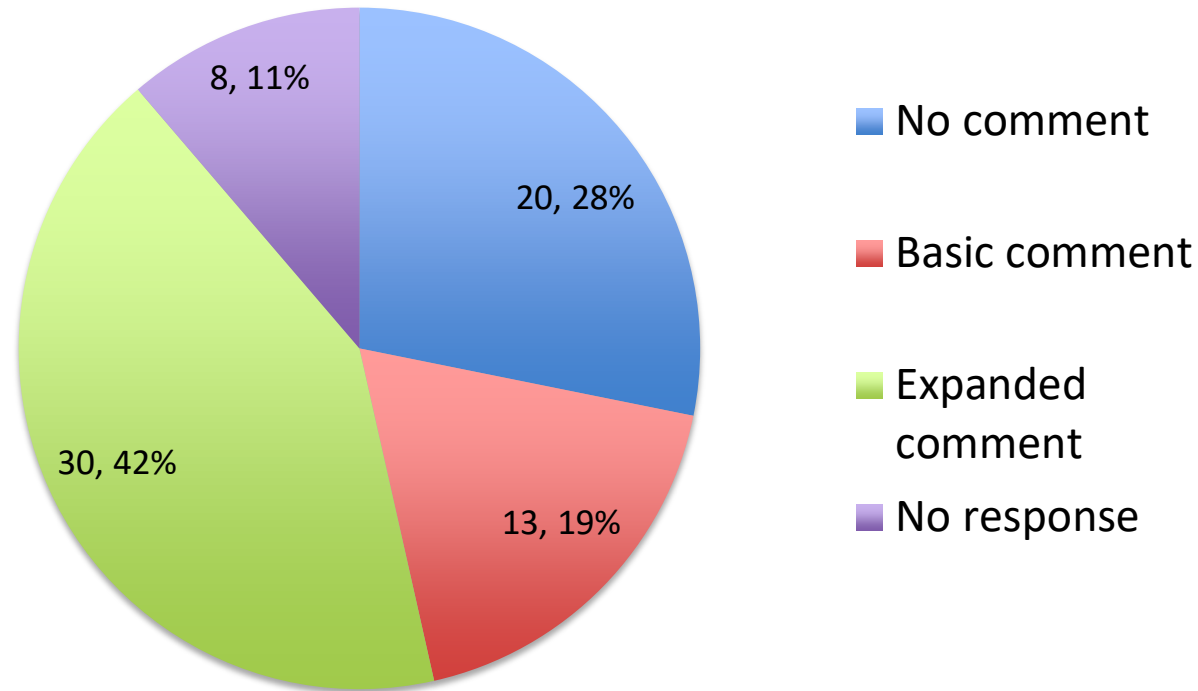
9 (a) Roche users: What cut-off value for FSH do you use to advise if a woman has entered the perimenopause?



9(b) Beckman users: What cut-off value for FSH do you use to advise if a woman has entered the perimenopause?



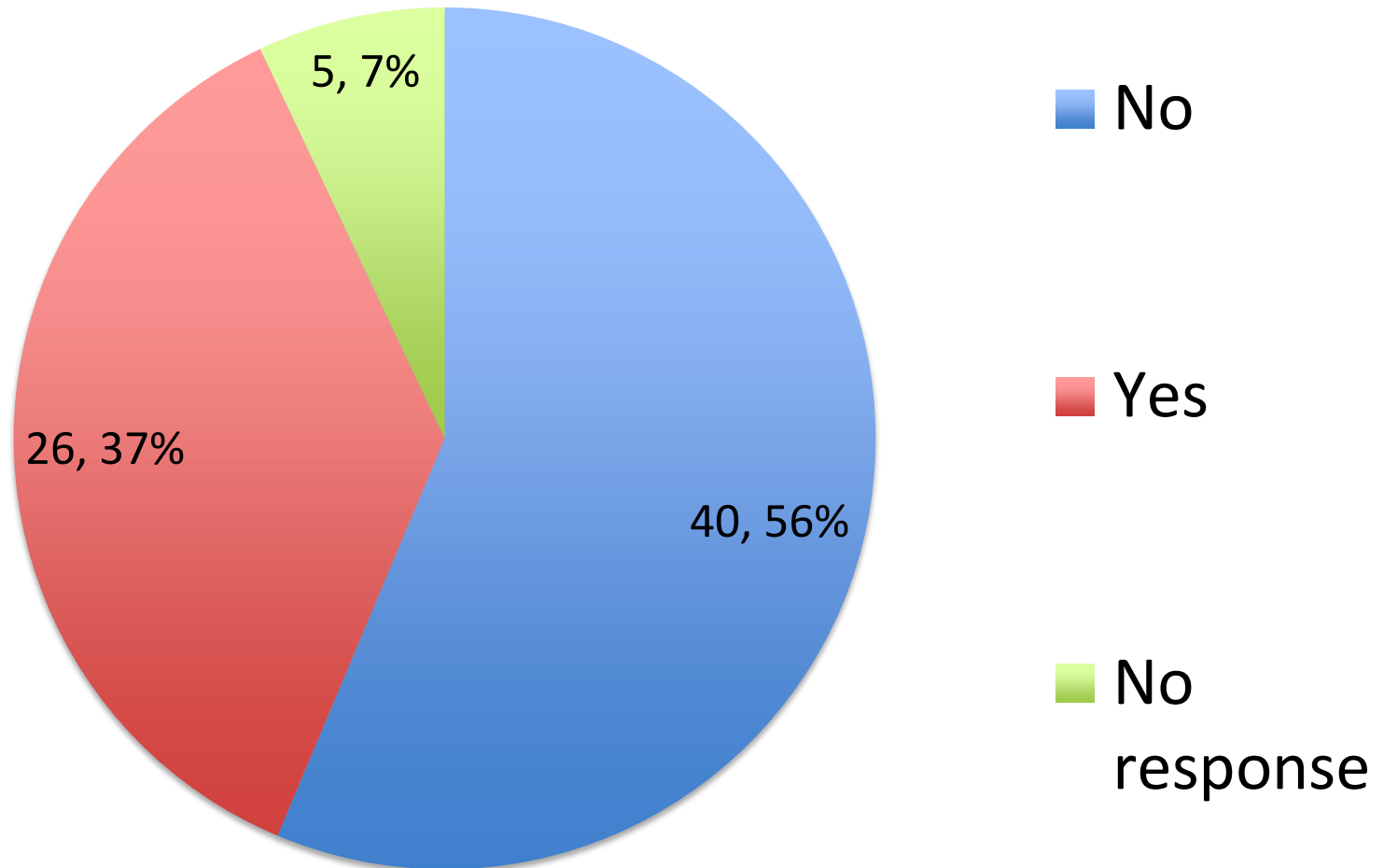
10) What comment(s) do you add when a woman has entered the perimenopause?



Basic comment : Consistent with the perimenopause

Expanded comment : FSH may fluctuate in the perimenopausal period with both fertile and infertile cycles. FSH should not be used as a basis for advice on contraception.

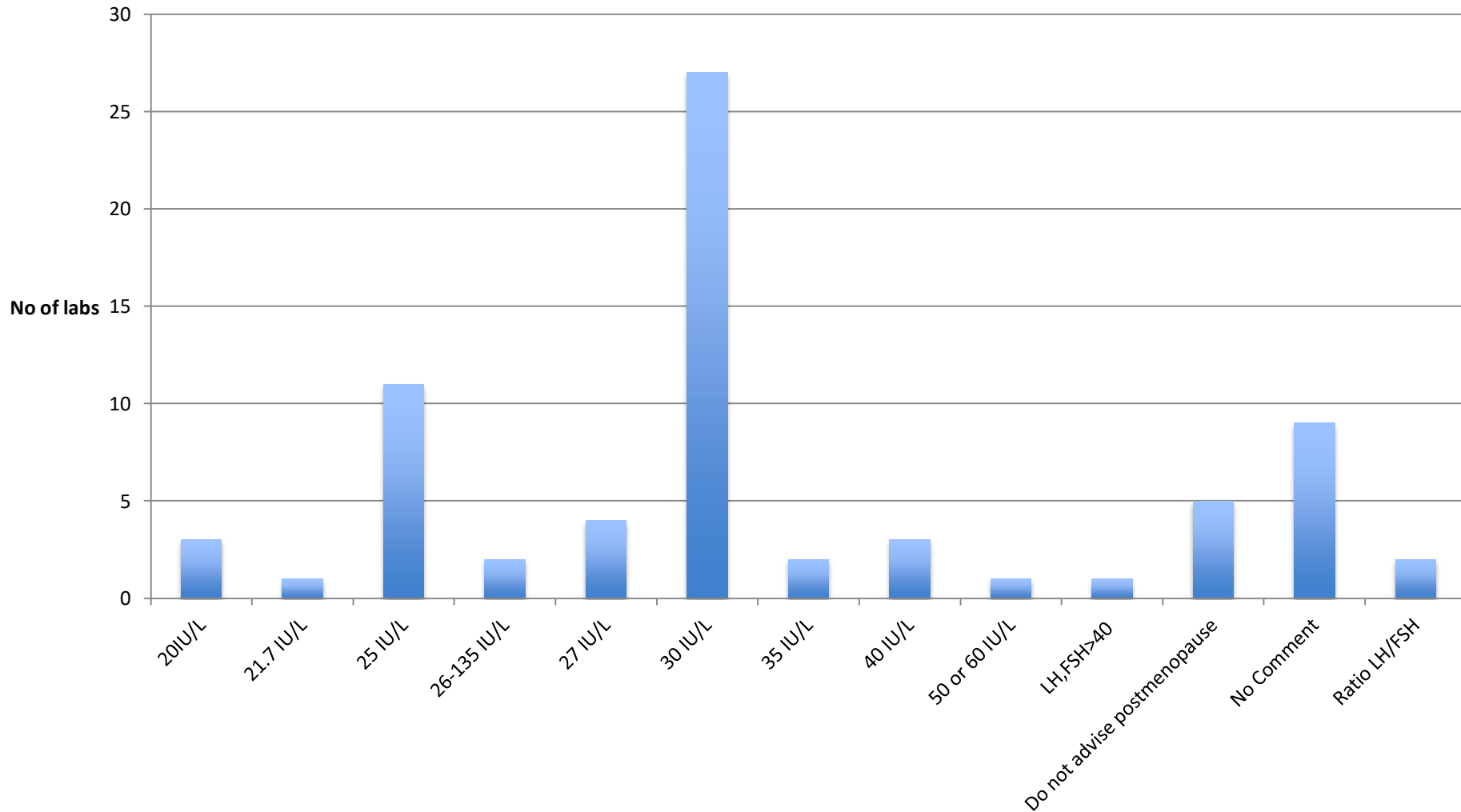
11) Do you have different comments for results in women <40 years?



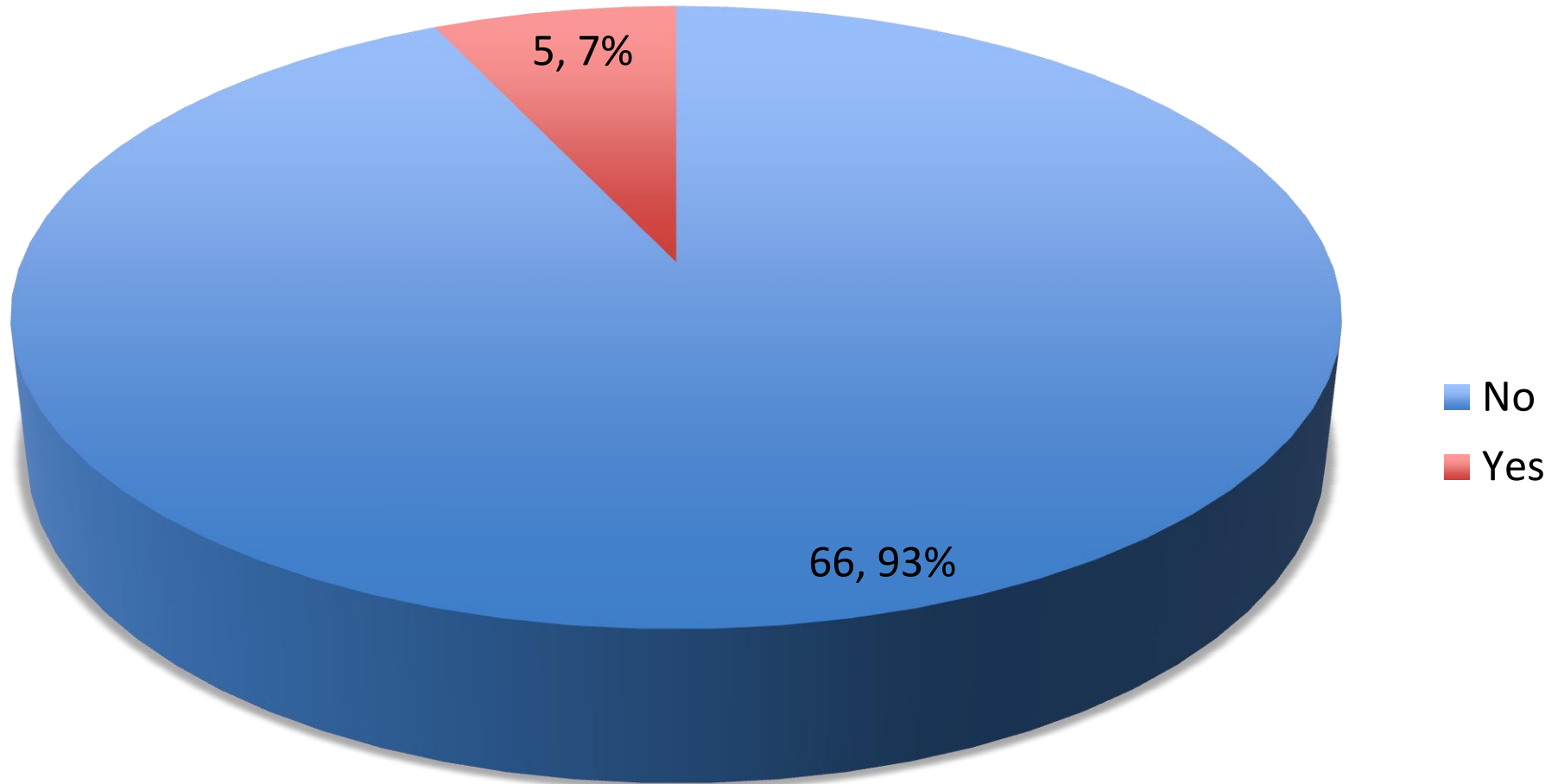
11 a) If yes, please give details below (sample of comments)

- Consistent with early ovarian failure, suggest repeat in 6-8 weeks to confirm.
- Consistent with premature menopause/perimenopause
- Premature menopause is the term usually applied to <40y.

12) What cut-off value for FSH do you use to advise if a woman has entered the postmenopausal state?



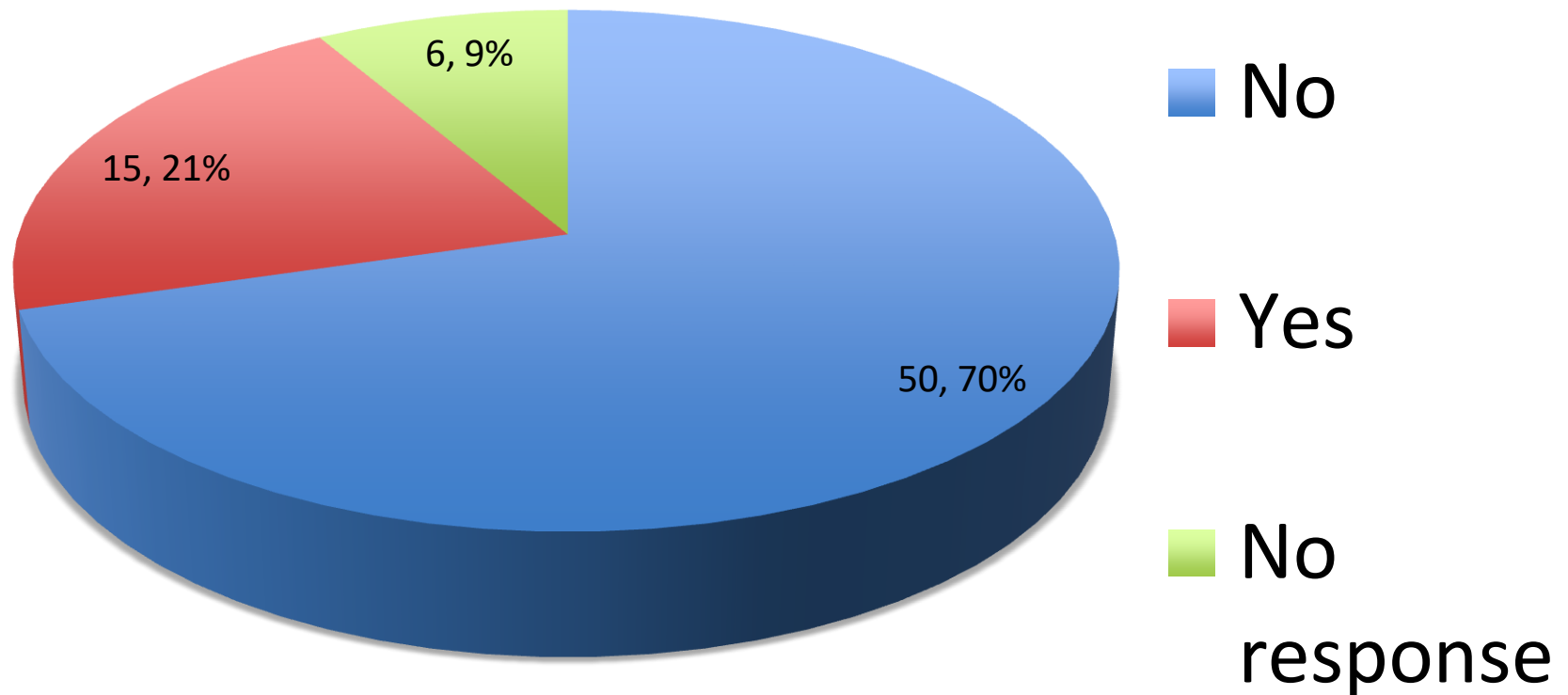
13) Do you have rules-based order communications for gonadotrophin requests for samples where evidence is being sought for the postmenopausal?



13 (a) If yes, please give details below

- All Gn requests add a test which goes to clinical approval - tests then added by duty biochemist as appropriate.
- For females aged 15-50 years the requestor is prompted to enter the date of the LMP, FSH is requested as the first line test and if this is over 15 IU/L an LH is added automatically
- Menopause profile. Front line FSH, LH is added if FSH 13-40 IU/L

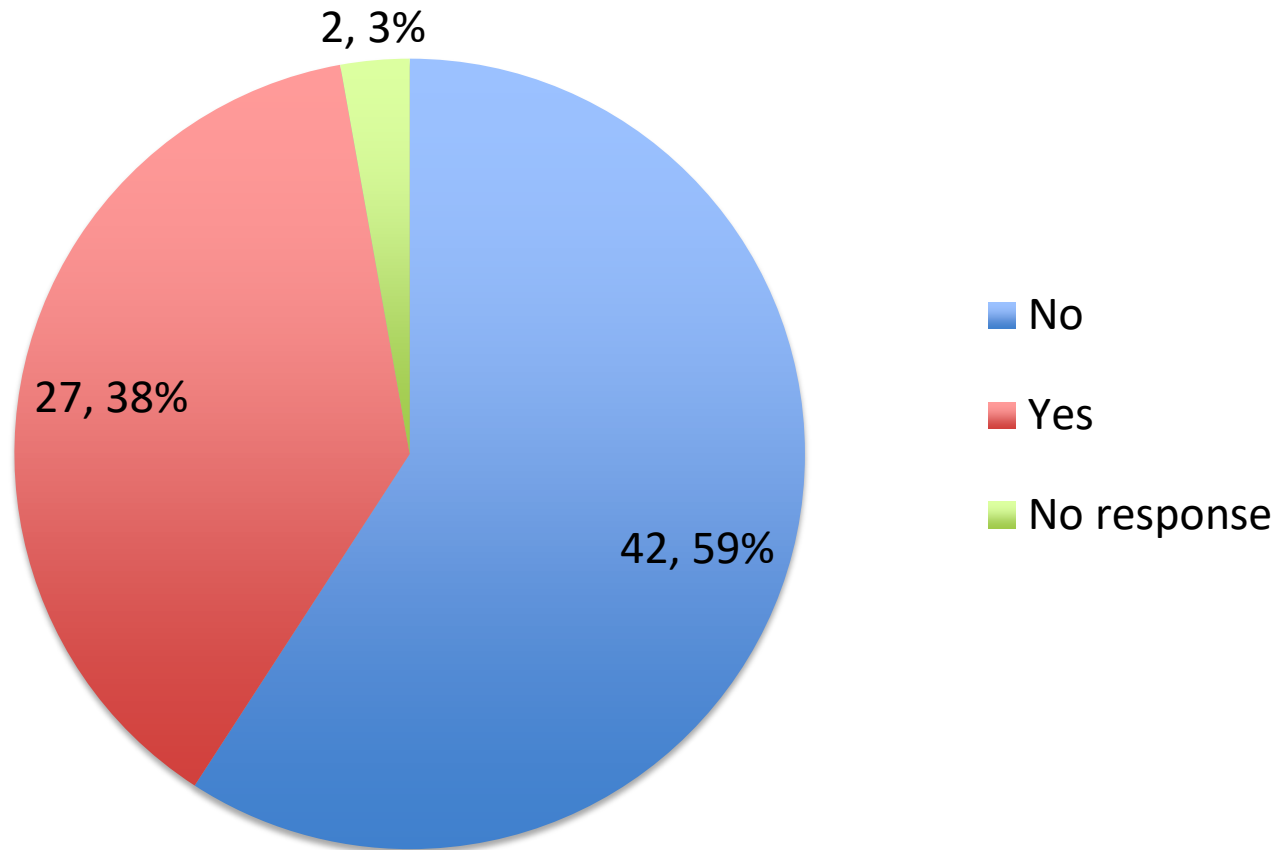
14) Do you offer advice on when the menopause has taken place?



14 a) If yes, what advice do you give? (sample of comments)

- Gonadotrophin pattern consistent with the menopause. Future fertile cycles not excluded - menopause is a clinical diagnosis.
- If asked we would advise that post-menopause is a clinical assessment and ask about time since last menses.
- We would advise that fertile cycles can occur up to and including the final cycle. If asked would advise that the menopause is a clinical diagnosis requiring 12 months of amenorrhoea before confirmed.
- If clinical details are available we add a comment :
Gonadotrophins consistent with menopause If FSH >30 considered to be post-menopausal
- If LMP >6 months ago, increased FSH suggests post-menopausal levels. Otherwise, perimenopausal levels.

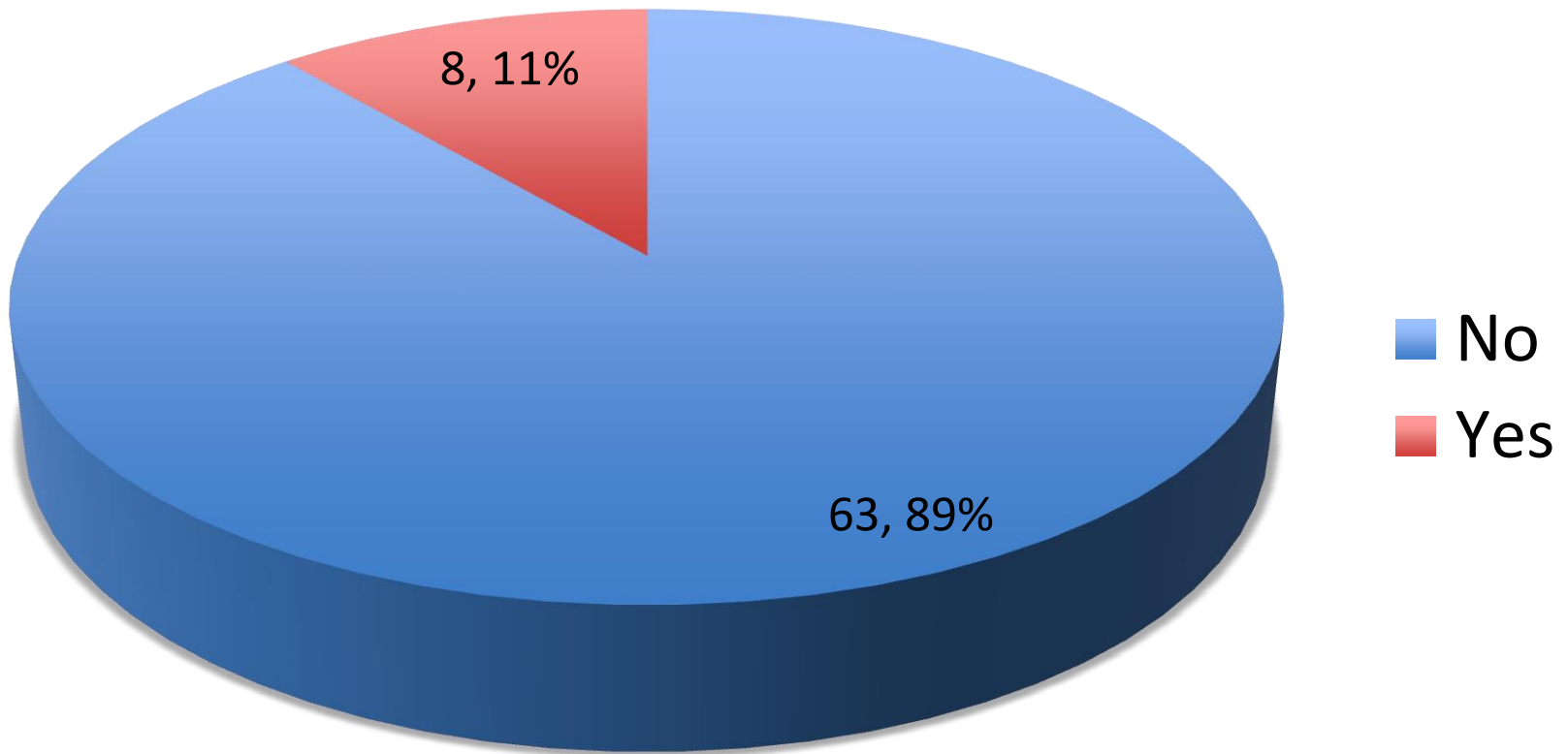
15) If you obtain a normal result for gonadotrophins in a woman in whom the menopause is being queried (with respect to follicular phase levels), do you add a comment?



16 If yes, please state time interval

- 2 weeks a part
- FSH on 2 occasions at least 1 month a part
- 6 weeks later
- 6-8 weeks
- At least three months based on clinical grounds
- Suggest repeat in 6 months
- Sometimes if the pattern in first sample suggestive and sample was not taken during days 1-5 of the cycle
- If female is >55 years then may ? pituitary problem.

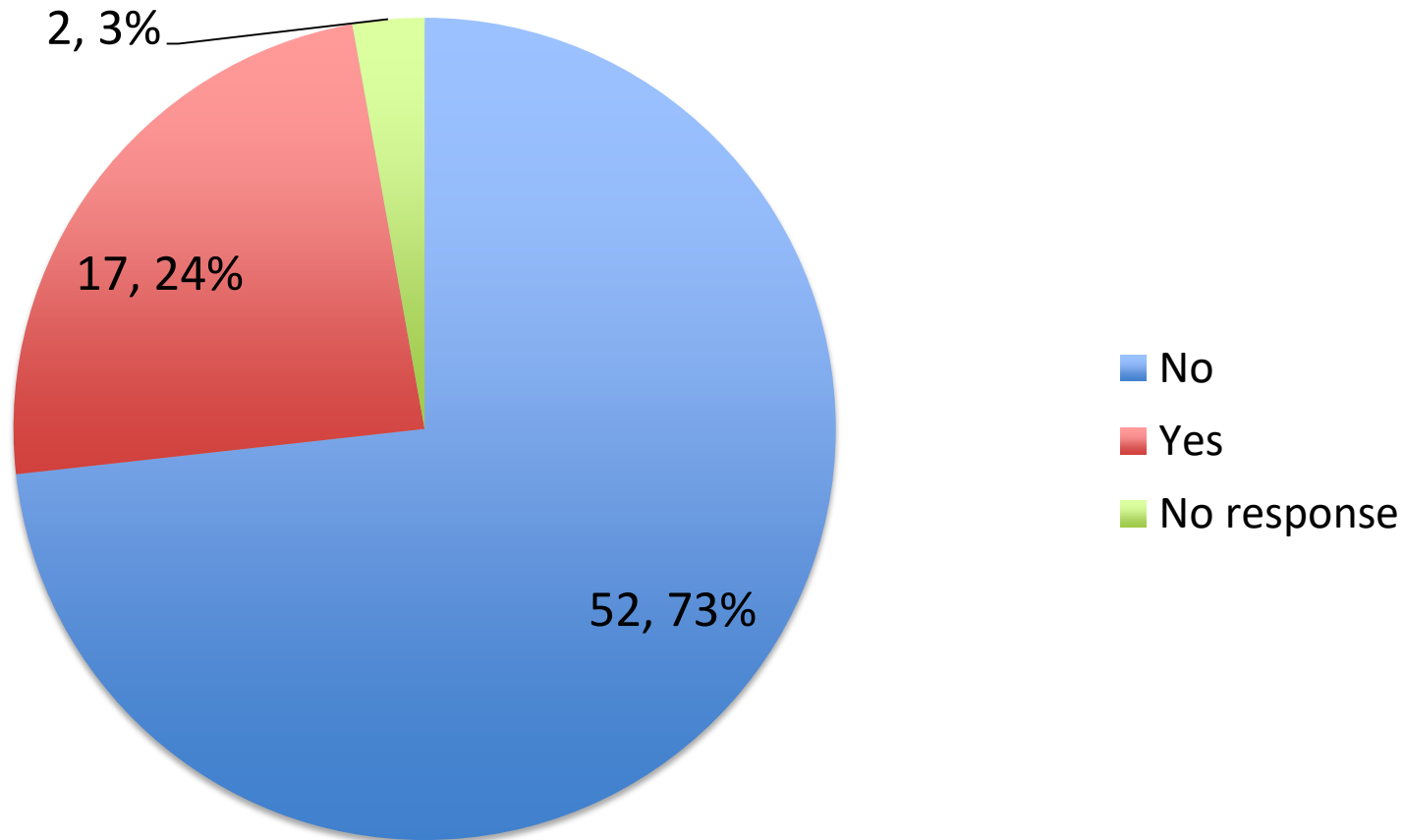
17) Do you offer advice on the use of gonadotrophins to assess response to HRT?



17) Do you offer advice on the use of gonadotrophins to assess response to HRT? (sample of comments)

- Only if asked
- Of limited value
- Gonadotrophins should not be measured in patients receiving oral hormone replacement therapy (HRT).
- If monitoring HRT efficacy, request E2. Gn not a reliable indicator
- Only that gonadotrophins can be unreliable markers for use in monitoring the efficacy of HRT and suggest monitoring treatment by oestradiol level (if patch/implant) and improvement in clinical symptoms.
- Do not recommend gonadotrophin testing for monitoring response to HRT (except E2 implants).
- Very occasional request and if type of HRT not specified would enquire and make appropriate comment .

Q 18 Do you offer advice on the use of gonadotrophin levels in the decision to withdraw contraception?



Do you offer advice on the use of gonadotrophin levels in the decision to withdraw contraception?

- At discretion of the duty biochemist when reporting but comments rarely added. GPs have been advised to use FSH if patient on depo/Mirena comment says NB contraception should be continued for one year after the onset of the menopause (2 years if under 50)
- Don't use levels FSH in postmenopausal range. Further fertile cycles cannot be excluded.
- Please note menopause is a clinical diagnosis based on absence of menstruation for one year. FSH may fluctuate a lot in the perimenopausal period with both fertile and infertile cycles.
- See best practice guidance on future contraception at
The faculty of sexual and reproductive health at <http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf>

Women over the age of 50 years who are amenorrhoeic and wish to stop POC can have their FSH levels checked. If the level is ≥ 30 IU/L the FSH should be repeated after 6 weeks. If the second FSH level is ≥ 30 IU/L contraception can be stopped after 1 year. Otherwise FSH(/LH) of no value in assessing the need for further contraception.

Conclusion

- There appeared to be a low response rate to the questionnaire with only 71/200 labs responding, however the impact of laboratory consolidation was not assessed and therefore its impact on the conclusions that can be assessed.
- There was a substantial difference in practice reported across the UK.
- Differences in the cut-off used by labs to define the perimenopause and post menopause were observed and recognized by NICE.

Conclusions 2

- The laboratory may be able to offer advice about whether a women has entered the perimenopause but defining the menopause biochemically is not possible-this is a clinical diagnosis.
- In view of the publication of draft guidelines from NICE we should soon be in a position to draw up national guidelines including specific recommendations for testing of women <40.

In summary from NICE

- Diagnosis carries an opportunity cost, with the resources used for it unavailable for alternative use within the NHS.
- Therefore, it is important that diagnosis ultimately leads to improved management and outcomes.
- The guideline group were not persuaded by the clinical evidence alone that there was a place for the routine use of biochemical, hormonal tests or ultrasound test in the diagnosis of menopause.
- Therefore, it is reasonable to conclude that such tests do not represent an efficient use of scarce NHS resources.