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# Global Practice Patterns in the Evaluation of Non-Obstructive Azoospermia: Results of a World-Wide Survey and Expert Recommendations

Rupin Shah<sup>1,2</sup>, Amarnath Rambhatla<sup>2,3</sup>, Widi Atmoko<sup>2,4</sup>, Marlon Martinez<sup>2,5</sup>, Imad Ziouziou<sup>2,6</sup>, Priyank Kothari<sup>2,7</sup>, Nicholas Tadros<sup>2,8</sup>, Nguyen Ho Vinh Phuoc<sup>2,9</sup>, Parviz Kavoussi<sup>2,10</sup>, Ahmed Harraz<sup>2,11,12,13</sup>, Gianmaria Salvio<sup>2,14</sup>, Murat Gul<sup>2,15</sup>, Taha Hamoda<sup>2,16,17</sup>, Tuncay Toprak<sup>2,18</sup>, Ponco Birowo<sup>2,4</sup>, Edmund Ko<sup>2,19</sup>, Mohamed Arafa<sup>2,20,21,22</sup>, Ramy Abou Ghayda<sup>2,23</sup>, Vilvopathy Senguttuvan Karthikeyan<sup>2,24</sup>, Ramadan Saleh<sup>2,25</sup>, Giorgio Ivan Russo<sup>2,26</sup>, Germar-Michael Pinggera<sup>2,27</sup>, Eric Chung<sup>2,28</sup>, Missy Savira<sup>2,6</sup>, Giovanni M. Colpi<sup>2,29</sup>, Wael Zohdy<sup>2,30</sup>, Edoardo Pescatori<sup>2,31</sup>, Hyun Jun Park<sup>2,32,33</sup>, Shinichiro Fukuhara<sup>2,34</sup>, Akira Tsujimura<sup>2,35</sup>, Cesar Rojas-Cruz<sup>2,36</sup>, Angelo Marino<sup>2,37</sup>, Siu King Mak<sup>2,38</sup>, Edouard Amar<sup>2,39</sup>, Wael Ibrahim<sup>2,40</sup>, Puneet Sindhvani<sup>2,41</sup>, Naif Alhathal<sup>2,42</sup>, Gian Maria Busetto<sup>2,43</sup>, Manaf Al Hashimi<sup>2,44,45</sup>, Ahmed El-Sakka<sup>2,46</sup>, Asci Ramazan<sup>2,47</sup>, Fotios Dimitriadis<sup>2,48</sup>, Massimiliano Timpano<sup>2,49</sup>, Davor Jezek<sup>2,50</sup>, Baris Altay<sup>2,51</sup>, Daniel Suslik Zylbersztejn<sup>2,52</sup>, Michael YC Wong<sup>2,53</sup>, Du Geon Moon<sup>2,54</sup>, Christine Wyns<sup>2,55</sup>, Safar Gamidov<sup>2,56</sup>, Hamed Akhavizadegan<sup>2,57</sup>, Alessandro Franceschelli<sup>2,58</sup>, Kaan Aydos<sup>2,59</sup>, Vinh Nguyen Quang<sup>2,60,61</sup>, Shedeed Ashour<sup>2,30</sup>, Adel Al Dayel<sup>2,62</sup>, Mohamed S. Al-Marhoon<sup>2,63</sup>, Sava Micic<sup>2,64</sup>, Saleh Binsaleh<sup>2,65</sup>, Alayman Hussein<sup>2,17</sup>, Haitham Elbardisi<sup>2,21,22</sup>, Taymour Mostafa<sup>2,30</sup>, Emad Taha<sup>2,16,17</sup>, Jonathan Ramsay<sup>2,66</sup>, Athanasios Zachariou<sup>2,67</sup>, Islam Fathy Soliman Abdelrahman<sup>2,30,68</sup>, Osvaldo Rajmil<sup>2,69</sup>, Arif Kalkanli<sup>2,70</sup>, Juan Manuel Corral Molina<sup>2,71</sup>, Kadir Bocu<sup>2,72</sup>, Gede Wirya Kusuma Duarsa<sup>2,73</sup>, Gokhan Ceker<sup>2,74</sup>, Ege Can Serefoglu<sup>2,75</sup>, Fahmi Bahar<sup>2,76</sup>, Nazim Gherabi<sup>2,77</sup>, Shinnosuke Kuroda<sup>2,78</sup>, Abderrazak Bouzouita<sup>2,79</sup>, Ahmet Gudeloglu<sup>2,80</sup>, Erman Ceyhan<sup>2,81</sup>, Mohamed Saeed Mohamed Hasan<sup>2,82</sup>, Muhammad Ujudud Musa<sup>2,83</sup>, Ahmad Motawi<sup>2,30</sup>, Cho Chak-Lam<sup>2,84</sup>, Hisanori Taniguchi<sup>2,85</sup>, Christopher Chee Kong Ho<sup>2,86</sup>, Jesus Fernando Solorzano Vazquez<sup>2,87</sup>, Shingai Mutambirwa<sup>2,88</sup>, Nur Dokuzeylul Gungor<sup>2,89</sup>, Marion Bendayan<sup>2,90,91</sup>, Carlo Giulioni<sup>2,92</sup>, Aykut Baser<sup>2,93</sup>, Marco Falcone<sup>2,49</sup>, Luca Boeri<sup>2,94</sup>, Gideon Blecher<sup>2,95,96</sup>, Alireza Kheradmand<sup>2,97</sup>, Tamilselvi Sethupathy<sup>2,98</sup>, Ricky Adriansjah<sup>2,99</sup>, Nima Narimani<sup>2,57</sup>, Charalampos Konstantinidis<sup>2,100</sup>, Tuan Thanh Nguyen<sup>2,101,102,103</sup>, Andrian Japari<sup>2,104</sup>, Parisa Dolati<sup>2,105</sup>, Keerti Singh<sup>2,106,107</sup>, Cevahir Ozer<sup>2,81</sup>, Selcuk Sarikaya<sup>2,108</sup>, Nadia Sheibak<sup>2,109,110</sup>, Ndagijimana Jean Bosco<sup>2,111</sup>, Mehmet Serkan Özkent<sup>2,112</sup>, Sang Thanh Le<sup>2,9,104</sup>, Ioannis Sokolakis<sup>2,113</sup>, Darren Katz<sup>2,114,115,116</sup>, Ryan Smith<sup>2,117</sup>, Manh Nguyen Truong<sup>2,103</sup>, Tan V. Le<sup>2,102,118</sup>, Zhongwei Huang<sup>2,119</sup>, Muslim Dogan Deger<sup>2,120</sup>, Umut Arslan<sup>2,18</sup>, Gokhan Calik<sup>2,121</sup>, Giorgio Franco<sup>2,122</sup>, Ayman Rashed<sup>2,123</sup>, Oguzhan Kahraman<sup>2,59</sup>, Sotiris Andreadakis<sup>2,124</sup>, Rosadi Putra<sup>2,125</sup>, Giancarlo Balercia<sup>2,14</sup>, Kareim Khalafalla<sup>2,21,126</sup>, Rossella Cannarella<sup>2,20,127</sup>, Anh Đặng Tuấn<sup>2,128</sup>, Amr El Meliegy<sup>2,30</sup>, Birute Zilaitiene<sup>2,129</sup>, Marlene Lizbeth Zamora Ramirez<sup>2,130</sup>, Filippo Giaccone<sup>2,131</sup>

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Correspondence to: Ashok Agarwal  <https://orcid.org/0000-0003-0585-1026>

Global Andrology Forum, 130 West Juniper Lane, Moreland Hills, OH 44022, USA.

Tel: +1-216-312-5829, E-mail: [agarwaa32099@outlook.com](mailto:agarwaa32099@outlook.com), Website: <https://www.globalandrologyforum.com>

Aldo E. Calogero<sup>2,26</sup>, Konstantinos Makarounis<sup>2,132</sup>, Sunil Jindal<sup>2,133</sup>, Bac Nguyen Hoai<sup>2,134</sup>, Ravi Banthia<sup>2,135</sup>, Marcelo Rodriguez Peña<sup>2,136</sup>, Dharani Moorthy<sup>2,137</sup>, Aram Adamyan<sup>2,138</sup>, Deniz Kulaksiz<sup>2,139</sup>, Hussein Kandil<sup>2,140</sup>, Nikolaos Sofikitis<sup>2,67</sup>, Ciro Salzano<sup>2,141</sup>, Andreas Jungwirth<sup>2,142</sup>, Surendra Reddy Banka<sup>2,143</sup>, Tiago Cesar Mierzwa<sup>2,144</sup>, Tahsin Turunç<sup>2,145</sup>, Divyanu Jain<sup>2,146</sup>, Armen Avoyan<sup>2,138</sup>, Pietro Salacone<sup>2,147</sup>, Ateş Kadioğlu<sup>2,148</sup>, Chirag Gupta<sup>2,149</sup>, Haocheng Lin<sup>2,150</sup>, Iman Shamohammadi<sup>2,151</sup>, Nasser Mogharabian<sup>2,152</sup>, Trenton Barrett<sup>2,153</sup>, Yavuz Onur Danacioğlu<sup>2,154</sup>, Andrea Crafa<sup>2,26</sup>, Salima Daoud<sup>2,155</sup>, Vineet Malhotra<sup>2,156</sup>, Abdulmalik Almardawi<sup>2,157</sup>, Osama Mohamed Selim<sup>2,30</sup>, Mohamad Moussa<sup>2,158,159</sup>, Saeid Haghdani<sup>2,160</sup>, Mesut Berkan Duran<sup>2,161</sup>, Yannic Kunz<sup>2,27</sup>, Mirko Preto<sup>2,49</sup>, Elena Eugeni<sup>2,162,163</sup>, Thang Nguyen<sup>2,134</sup>, Ahmed Rashad Elshahid<sup>2,82</sup>, Seso Sulijaya Suyono<sup>2,164</sup>, Dyandra Parikesit<sup>2,165</sup>, Essam Nada<sup>2,25</sup>, Eduardo Gutiérrez Orozco<sup>2,166</sup>, Florence Boitrelle<sup>2,90,91</sup>, Nguyen Thi Minh Trang<sup>2,102</sup>, Mounir Jamali<sup>2,167</sup>, Raju Nair<sup>2,168</sup>, Mikhail Ruzaev<sup>2,169</sup>, Franco Gadda<sup>2,94</sup>, Charalampos Thomas<sup>2,100</sup>, Raphael Henrique Ferreira<sup>2,170</sup>, Umit Gul<sup>2,171</sup>, Serena Maruccia<sup>2,172</sup>, Ajay Kanbur<sup>2,173,174</sup>, Ella Kinzikeeva<sup>2,175</sup>, Saad Abumelha<sup>2,16</sup>, Nguyen Quang<sup>2,60,61</sup>, Raghavender Kosgi<sup>2,176</sup>, Fatih Gokalp<sup>2,177</sup>, Mohammad Ayodhia Soebadi<sup>2,178</sup>, Gustavo Marquesine Paul<sup>2,179</sup>, Hesamoddin Sajadi<sup>2,180</sup>, Deepak Gupte<sup>2,181</sup>, Rafael F. Ambar<sup>2,52,144</sup>, Emrullah Sogutdelen<sup>2,182</sup>, Karun Singla<sup>2,183</sup>, Ari Basurkano<sup>2,184</sup>, Shannon Hee Kyung Kim<sup>2,185,186</sup>, Mohammad Ali Sadighi Gilani<sup>2,180</sup>, Koichi Nagao<sup>2,187</sup>, Sakti Ronggowardhana Brodjonegoro<sup>2,188</sup>, Andri Rezano<sup>2,189,190</sup>, Mohamed Elkhoully<sup>2,191</sup>, Rossella Mazzilli<sup>2,192</sup>, Hasan M. A. Farsi<sup>2,16</sup>, Hung Nguyen Ba<sup>2,193</sup>, Hamed Alali<sup>2,194</sup>, Dimitrios Kafetzis<sup>2,195</sup>, Tran Quang Tien Long<sup>2,196</sup>, Sami Alsaid<sup>2,21</sup>, Hoang Bao Ngoc Cuong<sup>2,197</sup>, Knigavko Oleksandr<sup>2,198</sup>, Akhmad Mustafa<sup>2,99</sup>, Herik Acosta<sup>2,199</sup>, Hrishikesh Pai<sup>2,200</sup>, Bahadır Şahin<sup>2,201</sup>, Eko Arianto<sup>2,202</sup>, Colin Teo<sup>2,203</sup>, Sanjay Prakash Jayaprakash<sup>2,24</sup>, Rinaldo Indra Rachman<sup>2,4</sup>, Mustafa Gurkan Yenice<sup>2,154</sup>, Omar Sefrioui<sup>2,204</sup>, Smit Paghdar<sup>2,205</sup>, Shivam Priyadarshi<sup>2,206</sup>, Marko Tanic<sup>2,207</sup>, Noor Kareem Alfatlawy<sup>2,208</sup>, Fikri Rizaldi<sup>2,178</sup>, Ranjit B. Vishwakarma<sup>1,2</sup>, George Kanakis<sup>2,209</sup>, Dinesh Thomas Cherian<sup>2,210</sup>, Joe Lee<sup>2,211</sup>, Raisa Galstyan<sup>2,212</sup>, Hakan Keskin<sup>2,80</sup>, Jana Wurzachner<sup>2,27</sup>, Doddy Hami Seno<sup>2,213</sup>, Bambang S. Noegroho<sup>2,99</sup>, Ria Margiana<sup>2,214,215,216</sup>, Qaisar Javed<sup>2,217</sup>, Fabrizio Castiglioni<sup>2,218</sup>, Raman Tanwar<sup>2,219</sup>, Ana Puigvert<sup>2,220</sup>, Coşkun Kaya<sup>2,221</sup>, Medianto Purnomo<sup>2,222</sup>, Chadi Yazbeck<sup>2,223</sup>, Azwar Amir<sup>2,224</sup>, Edson Borges<sup>2,225</sup>, Marina Bellavia<sup>2,29</sup>, Isaac Ardianson Deswanto<sup>2,6</sup>, Vinod K V<sup>2,226</sup>, Giovanni Liguori<sup>2,227</sup>, Dang Hoang Minh<sup>2,61</sup>, Kashif Siddiqi<sup>2,228</sup>, Fulvio Colombo<sup>2,31</sup>, Armand Zini<sup>2,229</sup>, Niket Patel<sup>2,230</sup>, Selahittin Çayan<sup>2,231</sup>, Ula Al-Kawaz<sup>2,232</sup>, Maged Ragab<sup>2,233</sup>, Charalampos Konstantinidis<sup>2,234</sup>, Guadalupe Hernández Hebrard<sup>2,235</sup>, Ivan Hoffmann<sup>2,236,237</sup>, Ozan Efesoy<sup>2,238</sup>, Barış Saylam<sup>2,238</sup>, Ashok Agarwal<sup>2,20</sup>

<sup>1</sup>Division of Andrology, Department of Urology, Lilavati Hospital and Research Centre, Mumbai, India, <sup>2</sup>Global Andrology Forum, Moreland Hills, OH, <sup>3</sup>Department of Urology, Henry Ford Health System, Vattikuti Urology Institute, Detroit, MI, USA, <sup>4</sup>Department of Urology, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, <sup>5</sup>Section of Urology, Department of Surgery, University of Santo Tomas Hospital, Manila, Philippines, <sup>6</sup>Department of Urology, College of Medicine and Pharmacy, Ibn Zohr University, Agadir, Morocco, <sup>7</sup>Department of Urology, B.Y.L Nair Ch Hospital, Topiwala National Medical College, Mumbai, India, <sup>8</sup>Division of Urology, Southern Illinois University School of Medicine, Springfield, IL, USA, <sup>9</sup>Department of Andrology, Binh Dan Hospital, Ho Chi Minh City, Vietnam, <sup>10</sup>Department of Reproductive Urology, Austin Fertility & Reproductive Medicine/Westlake IVF, Austin, TX, USA, <sup>11</sup>Department of Urology, Mansoura University Urology and Nephrology Center, Mansoura, Egypt, <sup>12</sup>Department of Surgery, Urology Unit, Farwaniya Hospital, Farwaniya, <sup>13</sup>Department of Urology, Sabah Al Ahmad Urology Center, Kuwait City, Kuwait, <sup>14</sup>Department of Endocrinology, Polytechnic University of Marche, Ancona, Italy, <sup>15</sup>Department of Urology, Selçuk University School of Medicine, Konya, Turkey, <sup>16</sup>Department of Urology, King Abdulaziz University, Jeddah, Saudi Arabia, <sup>17</sup>Department of Andrology, Faculty of Medicine, Assiut University, Assyut, Egypt, <sup>18</sup>Department of Urology, Fatih Sultan Mehmet Training and Research Hospital, University of Health Sciences, Istanbul, Turkey, <sup>19</sup>Department of Urology, Loma Linda University Health, Loma Linda, CA, <sup>20</sup>American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA, <sup>21</sup>Department of Urology, Hamad Medical Corporation, Doha, <sup>22</sup>Department of Urology, Weill Cornell Medical-Qatar, Doha, Qatar, <sup>23</sup>Urology Institute, University Hospitals, Case Western Reserve University, Cleveland, OH, USA, <sup>24</sup>Andrology Unit, Department of Urology, Apollo Hospitals, Greaves Road, Chennai, India, <sup>25</sup>Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt, <sup>26</sup>Urology Section, University of Catania, Catania, Italy, <sup>27</sup>Department of Urology, University Hospital Innsbruck, Innsbruck, Austria, <sup>28</sup>Department of Urology, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia, <sup>29</sup>Andrology and IVF Center, Next Fertility Procrea, Lugano, Switzerland, <sup>30</sup>Department of Andrology, Sexology & STIs, Faculty of Medicine, Cairo University, Cairo, Egypt, <sup>31</sup>Andrology and Reproductive Medicine Unit, Gynepro Medical, Bologna, Italy, <sup>32</sup>Department of Urology, Pusan National University School

of Medicine, Busan, <sup>33</sup>Medical Research Institute of Pusan National University Hospital, Busan, Korea, <sup>34</sup>Department of Urology, Graduate School of Medicine, Osaka University, Osaka, <sup>35</sup>Department of Urology, Juntendo University Urayasu Hospital, Chiba, Japan, <sup>36</sup>Department of Urology, University Hospital of Rostock, Rostock, Germany, <sup>37</sup>Reproductive Medicine Unit, ANDROS Day Surgery Clinic, Palermo, Italy, <sup>38</sup>Union Hospital, Hong Kong SAR, China, <sup>39</sup>Department of Urology, American Hospital of Paris, Paris, France, <sup>40</sup>Department of Obstetrics Gynaecology and Reproductive Medicine, Fertility Care Center in Cairo, Cairo, Egypt, <sup>41</sup>Department of Urology, College of Medicine and Life Sciences, University of Toledo, Toledo, OH, USA, <sup>42</sup>King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, <sup>43</sup>Department of Urology and Organ Transplantation, University of Foggia, Foggia, Italy, <sup>44</sup>Department of Urology, Burjeel Hospital, Abu Dhabi, <sup>45</sup>Department of Urology, Khalifa University College of Medicine and Health Science, Abu Dhabi, UAE, <sup>46</sup>Department of Urology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt, <sup>47</sup>Department of Urology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey, <sup>48</sup>1st Urology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece, <sup>49</sup>Department of Urology, Molinette Hospital, A.O.U. Città della Salute e della Scienza, University of Turin, Torino, Italy, <sup>50</sup>Department for Transfusion Medicine and Transplantation Biology, Reproductive Tissue Bank, University of Zagreb School of Medicine, Zagreb, Croatia, <sup>51</sup>Department of Urology, Ege University Medical School, Bornova, Izmir, Turkey, <sup>52</sup>Department of Urology, Fleury Group and Hospital Israelita Albert Einstein, São Paulo, Brazil, <sup>53</sup>Department of Andrology, International Urology, Fertility and Gynecology Centre, Mount Elizabeth Hospital, Singapore, <sup>54</sup>Department of Urology, Korea University Guro Hospital, Seoul, Korea, <sup>55</sup>Department of Gynaecology-Andrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium, <sup>56</sup>V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology and Perinatology, Ministry of Health of Russia, Moscow, Russia, <sup>57</sup>Department of Urology, School of Medicine, Hasheminejad Kidney Center, Iran University of Medical Science, Tehran, Iran, <sup>58</sup>Andrology Unit, University Hospital S. Orsola, Bologna, Italy, <sup>59</sup>Department of Urology, Ankara University, Ankara, Turkey, <sup>60</sup>Center for Andrology and Sexual Medicine, Viet Duc University Hospital, Hanoi, <sup>61</sup>Department of Urology, Can Tho University of Medicine and Pharmacy Hospital, Can Tho, Vietnam, <sup>62</sup>Men's Health Clinic Dammam, Dammam, Saudi Arabia, <sup>63</sup>Division of Urology, Department of Surgery, Sultan Qaboos University, Muscat, Oman, <sup>64</sup>Department of Andrology, Uromedica Polyclinic, Belgrade, Serbia, <sup>65</sup>Division of Urology, Department of Surgery, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia, <sup>66</sup>Department of Andrology, Hammersmith Hospital, London, UK, <sup>67</sup>Department of Urology, Ioannina University School of Medicine, Ioannina, Greece, <sup>68</sup>Department of Andrology, Armed Forces College of Medicine, Cairo, Egypt, <sup>69</sup>Department of Andrology, Fundacio Puigvert, Barcelona, Spain, <sup>70</sup>Department of Urology, Taksim Education and Research Hospital, Istanbul, Turkey, <sup>71</sup>Department of Urology, Hospital Clínico de Barcelona, Barcelona, Spain, <sup>72</sup>Department of Urology, Niğde Omer Halis Demir University Faculty of Medicine, Niğde, Turkey, <sup>73</sup>Department of Urology, Udayana University, Denpasar, Indonesia, <sup>74</sup>Department of Urology, Başakşehir Çam and Sakura City Hospital, Istanbul, <sup>75</sup>Department of Urology, Biruni University School of Medicine, Istanbul, Turkey, <sup>76</sup>Andrology Section, Siloam Sriwijaya Hospital, Palembang, Indonesia, <sup>77</sup>Department of Medicine, University of Algiers 1, Algiers, Algeria, <sup>78</sup>Department of Urology, Glickman Urological & Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH, USA, <sup>79</sup>Department of Anatomy, Faculty of Medicine, Faculty Tunis Manar, Tunis, Tunisia, <sup>80</sup>Department of Urology, Hacettepe University Faculty of Medicine, Ankara, <sup>81</sup>Department of Urology, Faculty of Medicine, Baskent University, Ankara, Turkey, <sup>82</sup>Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, <sup>83</sup>Urology Unit, Department of Surgery, Federal Medical Center, Katsina State, Nigeria, <sup>84</sup>Department of Surgery, S. H. Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong, <sup>85</sup>Department of Urology and Andrology, Kansai Medical University, Osaka, Japan, <sup>86</sup>Department of Surgery, School of Medicine, Taylor's University, Selangor, Malaysia, <sup>87</sup>IVF Department, CITMER Reproductive Medicine, Mexico City, Mexico, <sup>88</sup>Department of Urology, Dr. George Mukhari Academic Hospital, Sefako Makgatho Health Science University, Medunsa, South Africa, <sup>89</sup>Department of Obstetrics and Gynecology, Reproductive Endocrinology and IVF Unit, School of Medicine, Bahcesehir University, Istanbul, Turkey, <sup>90</sup>Department of Reproductive Biology, Fertility Preservation, Andrology, CECOS, Poissy Hospital, Poissy, <sup>91</sup>Department of Biology, Reproduction, Epigenetics, Environment and Development, Paris Saclay University, UVSQ, INRAE, BREED, Jouy-en-Josas, France, <sup>92</sup>Department of Urology, Polytechnic University of Marche, Ancona, Italy, <sup>93</sup>Department of Urology, Faculty of Medicine, Bandırma Onyedi Eylül University, Balıkesir, Turkey, <sup>94</sup>Department of Urology, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, <sup>95</sup>Department of Surgery, School of Clinical Sciences, Monash University, Melbourne, <sup>96</sup>Department of Urology, The Alfred Hospital, Melbourne, Australia, <sup>97</sup>Department of Urology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, <sup>98</sup>Department of Obstetrics and Gynaecology, CK Medical Centre Hospital, Erode, India, <sup>99</sup>Department of Urology, Hasan Sadikin General Hospital, Faculty of Medicine of Padjadjaran University, Bandung, Indonesia, <sup>100</sup>Urology Department, General Hospital of Corinth, Corinth, Greece, <sup>101</sup>Department of Urology, University of California, Irvine, CA, USA, <sup>102</sup>Department of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, <sup>103</sup>Department of Urology, Cho Ray Hospital, Ho Chi Minh City, Vietnam, <sup>104</sup>Department of IVF, Fertility Clinic, Telogorejo Hospital, Semarang, Indonesia, <sup>105</sup>Department of Animal Science, Faculty of Agriculture, University of Shiraz, Shiraz, Iran, <sup>106</sup>Department of Preclinical and Health Sciences, Faculty of Medical Sciences, The University of West Indies, Cave Hill Campus, Bridgetown, <sup>107</sup>Windsor Medical Centre, Bridgetown, Barbados, <sup>108</sup>Department of Urology, Gulhane Research and Training Hospital, University of Health Sciences, Ankara, Turkey, <sup>109</sup>Department of Anatomical Sciences, Reproductive Sciences and Technology Research Center, Iran University of Medical Sciences, Tehran, <sup>110</sup>Shahid Akbarabadi Clinical Research Development Unit (ShACRDU), Iran University of Medical Sciences, Tehran, Iran, <sup>111</sup>Department of Dermatology, Venereology & Andrology, Faculty of Medicine, University of Alexandria, Alexandria, Egypt, <sup>112</sup>Department of Urology, Konya City Hospital, Konya, Turkey, <sup>113</sup>Department of Urology, Martha-Maria Hospital Nuremberg, Nuremberg, Germany, <sup>114</sup>Men's Health Melbourne, Victoria, <sup>115</sup>Department of Surgery, Western Precinct, University of Melbourne, Victoria, <sup>116</sup>Department of Urology, Western Health, Victoria, Australia, <sup>117</sup>Department of Urology, University of Virginia School of Medicine, Charlottesville, VA, USA, <sup>118</sup>Department of Urology and Andrology, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam, <sup>119</sup>Department of Obstetrics and Gynaecology, National University Health Systems, Singapore, <sup>120</sup>Department of Urology, Edirne Sultan 1st Murat State Hospital, Edirne, <sup>121</sup>Department of Urology, Istanbul Medipol University, Istanbul, Turkey, <sup>122</sup>Department of Urology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy, <sup>123</sup>Department of Urology, Faculty of Medicine, 6th of October University, Giza, Egypt, <sup>124</sup>Private



Practice, Thessaloniki, Greece, <sup>125</sup>Department of Urology, RSUD Ciawi Regional General Hospital, West Java, Indonesia, <sup>126</sup>Department of Urology, University of Illinois, Chicago, IL, USA, <sup>127</sup>Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy, <sup>128</sup>Tam Anh IVF Center, Tam Anh General Hospital, Hanoi, Vietnam, <sup>129</sup>Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania, <sup>130</sup>Reproductive Medicine Unit, Español Hospital, Mexico City, Mexico, <sup>131</sup>HERA Center, Unit of Reproductive Medicine, Sant'Agata Li Battiati, Catania, Italy, <sup>132</sup>Department of Urology and Andrology, Locus Medicus, Athens, Greece, <sup>133</sup>Department of Andrology & Reproductive Medicine, Jindal Hospital & Fertility Center, Meerut, India, <sup>134</sup>Department of Andrology and Sexual Medicine, Hanoi Medical University Hospital, Hanoi, Vietnam, <sup>135</sup>Department of Urology, Western General Hospital, Edinburgh, UK, <sup>136</sup>Instituto de Ginecología y Fertilidad (IFER), Universidad de Buenos Aires, Buenos Aires, Argentina, <sup>137</sup>IVF Department, Swarupa fertility & IVF Centre, Vijayawada, India, <sup>138</sup>Department of Urology, Astghik Medical Center, Yerevan, Armenia, <sup>139</sup>Department of Obstetrics and Gynecology, Kanuni Training and Research Hospital, University of Health Sciences, Trabzon, Turkey, <sup>140</sup>Fakih IVF Fertility Center, Abu Dhabi, UAE, <sup>141</sup>PO San Giovanni Bosco, ASL Napoli 1 Centro, Napoli, Italy, <sup>142</sup>St. Barbara Private Clinic, Bad Vigaun, Austria, <sup>143</sup>Department of Andrology, Androcare Institute of Andrology and Men's Health, Hyderabad, India, <sup>144</sup>Department of Urology, Centro Universitario em Saude do ABC, Santo André, Brazil, <sup>145</sup>Urology Clinic, Iskenderun Gelisim Hospital, Iskenderun, Turkey, <sup>146</sup>Department of Obstetrics and Gynecology, Jaipur Golden Hospital, New Delhi, India, <sup>147</sup>Andrology and Pathophysiology of Reproduction Unit, Santa Maria Goretti Hospital, Latina, Italy, <sup>148</sup>Section of Andrology, Department of Urology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, <sup>149</sup>Department of Urology, Jaipur National University, Jaipur, India, <sup>150</sup>Department of Urology, Peking University Third Hospital, Peking University, Beijing, China, <sup>151</sup>Department of Urology, Shiraz University of Medical Sciences, Shiraz, Iran, <sup>152</sup>Sexual Health and Fertility Research Center, Shahrood University of Medical Sciences, Shahrood, Iran, <sup>153</sup>Perth Urology Clinic, Perth, WA, Australia, <sup>154</sup>Department of Urology, Bakırköy Dr. Sadi Konuk Training and Research Hospital, University of Health Science Istanbul, Istanbul, Turkey, <sup>155</sup>Laboratory of Histo-Embryology and Reproductive Biology, Faculty of Medicine of Sfax, University of Sfax, Sfax, Tunisia, <sup>156</sup>Department of Urology and Andrology, VNA Hospital, New Delhi, India, <sup>157</sup>Department of Urology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia, <sup>158</sup>Department of Urology, Lebanese University, Beirut, <sup>159</sup>Department of Urology, Al Zahraa Hospital, UMC, Beirut, Lebanon, <sup>160</sup>Andrology Research Center, Yazd Reproductive Science Institute, Isfahan Fertility and Isfahan, Yazd, Iran, <sup>161</sup>Department of Urology, Pamukkale University School of Medicine, Denizli, Turkey, <sup>162</sup>Department of Medicine and Surgery, University of Perugia, Perugia, Italy, <sup>163</sup>Department of Medicine and Medical Specialties, Division of Medical Andrology and Endocrinology of Reproduction, University of Terni, Terni, Italy, <sup>164</sup>Gladiol IVF, Magelang, <sup>165</sup>Department of Urology, Universitas Indonesia Hospital, Faculty of Medicine, Universitas Indonesia, Depok, Indonesia, <sup>166</sup>IVF Department, CITMER Reproductive Medicine, Nuevo Leon, Mexico, <sup>167</sup>Department of Urology, Military Teaching Hospital, Rabat, Morocco, <sup>168</sup>Department of Reproductive Medicine, Mitera Hospital, Kottayam, India, <sup>169</sup>Urology Clinic, Moscow, Russia, <sup>170</sup>Department of Urology, Santa Casa de Ribeirão Preto, São Paulo, Brazil, <sup>171</sup>Private EPC Hospital, Adana, Turkey, <sup>172</sup>Department of Urology, ASST Santi Paolo e Carlo, San Paolo Hospital, Milano, Italy, <sup>173</sup>Department of Andrology, Kanbur Clinic, Thane, <sup>174</sup>Department of Urology, Jupiter Hospital, Thane, India, <sup>175</sup>Zucchi Clinical Institutes, Monza, Italy, <sup>176</sup>Department of Urology and Andrology, AIG Hospitals, Hyderabad, India, <sup>177</sup>Department of Urology, Faculty of Medicine, Hatay Mu Stafa Kemal University, Antakya, Turkey, <sup>178</sup>Department of Urology, Faculty of Medicine, Universitas Airlangga, Soetomo Hospital, Surabaya, Indonesia, <sup>179</sup>Department of Urology, Hospital de Clínicas of the Federal University of Paraná, Curitiba, Brazil, <sup>180</sup>Department of Andrology, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran, <sup>181</sup>Department of Urology, Bombay Hospital and Medical Research Center, Mumbai, <sup>182</sup>Department of Urology, Clarity Health, Chandigarh, India, <sup>183</sup>Department of Urology, Dr. Dradjat Hospital, Serang, Indonesia, <sup>184</sup>IVF Australia, Sydney, <sup>185</sup>Macquarie School of Medicine, Macquarie University, Sydney, Australia, <sup>186</sup>Department of Urology, Imperial Healthcare NHS Trust, Charing Cross Hospital, London, UK, <sup>187</sup>Department of Urology, Toho University Faculty of Medicine, Tokyo, Japan, <sup>188</sup>Division of Urology, Department of Surgery, Prof. Dr. Sardjito Hospital, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, <sup>189</sup>Andrology Study Program, Department of Biomedical Sciences, Faculty of Medicine, Universitas Airlangga, Surabaya, <sup>190</sup>Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia, <sup>191</sup>IVF Department, Bourn Hall Fertility Center, Dubai, UAE, <sup>192</sup>Unit of Endocrinology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy, <sup>193</sup>Andrology Unit, ART Center, Vinmec Times City International Hospital, Hanoi, Vietnam, <sup>194</sup>King Fahad Specialist Hospital, Dammam, Saudi Arabia, <sup>195</sup>Orchid IVF Clinic, Dubai, UAE, <sup>196</sup>Department of Obstetrics and Gynecology, Hanoi Obstetric and Gynecology Hospital, Hanoi, <sup>197</sup>Department of Surgery, Hai Phong University of Medicine and Pharmacy, Hai Phong, Vietnam, <sup>198</sup>Department of Urology, Nephrology and Andrology, Kharkiv National Medical University, Kharkiv, Ukraine, <sup>199</sup>Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan, <sup>200</sup>IVF Department, Bloom IVF Group, Mumbai, India, <sup>201</sup>Department of Urology, School of Medicine, Marmara University, İstanbul, Turkey, <sup>202</sup>Department of Urology, Prof R.D. Kandou Hospital, Manado, Indonesia, <sup>203</sup>Department of Urology, Gleneagles Hospital, Singapore, <sup>204</sup>African Fertility Center, Casablanca, Morocco, <sup>205</sup>UVA Urology Clinic in Charlottesville, UVA Specialty Care Clinic in Culpeper, Culpeper, VA, USA, <sup>206</sup>Department of Urology, Sawai Man Singh Medical College and Hospital, Jaipur, Rajasthan, India, <sup>207</sup>Department of Urology, General Hospital, Cuprija, Serbia, <sup>208</sup>Fertility Center of Al-Najaf/Al-Sadr Medical City, Babylon Health Directorate, Iraqi Ministry of Health, Baghdad, Iraq, <sup>209</sup>Department of Endocrinology, Diabetes and Metabolism, Athens Naval & VA Hospital, Athens, Greece, <sup>210</sup>Urology Department, Aster Medcity, Kochi, India, <sup>211</sup>Department of Urology, National University Hospital, Singapore, <sup>212</sup>Department of Urology, Yerevan State Medical University, Yerevan, Armenia, <sup>213</sup>Division of Urology, Department of Surgery, Persahabatan General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, <sup>214</sup>Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, <sup>215</sup>Master's Programme Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, <sup>216</sup>Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, <sup>217</sup>Department of Urology, Al-Ahlia Hospital, Abu Dhabi, UAE, <sup>218</sup>Andrology Unit, ART Center - San Carlo Clinic, Milan, Italy, <sup>219</sup>Urology Center, Jyoti Hospital, Gurugram, India, <sup>220</sup>Institute of Andrology and Sexual Medicine (IANDROMS), Barcelona, Spain, <sup>221</sup>Department of Urology, Health Science University Eskisehir City HPRH, Eskisehir, Turkey, <sup>222</sup>Department of Urology, Brawijaya University, Malang, Indonesia, <sup>223</sup>Department of Obstetrics Gynecology and Reproductive Medicine, Reprogynes Medical Institute, Paris, France, <sup>224</sup>Department of Urology, Dr Wahidin

Sudirohusodo Hospital, Makassar, Indonesia, <sup>225</sup>Fertility Assisted Fertilization Center, São Paulo, Brazil, <sup>226</sup>Department of Urology, Cure & SK Hospital, Trivandrum, India, <sup>227</sup>Department of Urology, University of Trieste, Trieste, Italy, <sup>228</sup>Department of Urology, Cleveland Clinic, Abu Dhabi, UAE, <sup>229</sup>Department of Surgery, McGill University, Montreal, QC, Canada, <sup>230</sup>Akanksha Hospital and Research Institute, Anand, Gujarat, India, <sup>231</sup>Department of Urology, University of Mersin School of Medicine, Mersin, Turkey, <sup>232</sup>High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq, <sup>233</sup>Department of Urology, Tanta University, Tanta, Egypt, <sup>234</sup>Urology and Neuro-Urology Unit, National Rehabilitation Center, Athens, Greece, <sup>235</sup>IVF Department, CITMER Reproductive Medicine, Puebla, Mexico, <sup>236</sup>Department of Reproductive Medicine and Andrology, University Clinic Halle (Saale), Halle, <sup>237</sup>Reproductive Center Dr. Hoffmann, Berlin, Germany, <sup>238</sup>Department of Urology, Mersin City Training and Research Hospital, University of Health Sciences, Mersin, Turkey

**Purpose:** Non-obstructive azoospermia (NOA) represents the persistent absence of sperm in ejaculate without obstruction, stemming from diverse disease processes. This survey explores global practices in NOA diagnosis, comparing them with guidelines and offering expert recommendations.

**Materials and Methods:** A 56-item questionnaire survey on NOA diagnosis and management was conducted globally from July to September 2022. This paper focuses on part 1, evaluating NOA diagnosis. Data from 367 participants across 49 countries were analyzed descriptively, with a Delphi process used for expert recommendations.

**Results:** Of 336 eligible responses, most participants were experienced attending physicians (70.93%). To diagnose azoospermia definitively, 81.7% requested two semen samples. Commonly ordered hormone tests included serum follicle-stimulating hormone (FSH) (97.0%), total testosterone (92.9%), and luteinizing hormone (86.9%). Genetic testing was requested by 66.6%, with karyotype analysis (86.2%) and Y chromosome microdeletions (88.3%) prevalent. Diagnostic testicular biopsy, distinguishing obstructive azoospermia (OA) from NOA, was not performed by 45.1%, while 34.6% did it selectively. Differentiation relied on physical examination (76.1%), serum hormone profiles (69.6%), and semen tests (68.1%). Expectations of finding sperm surgically were higher in men with normal FSH, larger testes, and a history of sperm in ejaculate.

**Conclusions:** This expert survey, encompassing 367 participants from 49 countries, unveils congruence with recommended guidelines in NOA diagnosis. However, noteworthy disparities in practices suggest a need for evidence-based, international consensus guidelines to standardize NOA evaluation, addressing existing gaps in professional recommendations.

**Key words:** Azoospermia; Diagnosis; Guideline; Infertility, male; Surveys and questionnaires

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## INTRODUCTION

Azoospermia is defined as the absence of spermatozoa in the ejaculate following centrifugation and subsequent microscopy of the specimen on 2 separate semen analyses [1,2]. Although it only affects 1%–2% of all men, the rate increases to 5%–15% among those seeking fertility evaluation or treatment [3,4]. Azoospermia can be broadly classified as obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) and each of them has different causes and management [5]. NOA results from impairment of testicular sperm production and constitutes around two-thirds of azoospermia cases [3].

NOA may result from a variety of causes ranging from genetic defects to acquired damage and is frequently unexplained [6]. Therefore, an adequate and appropriate workup for the patient with azoospermia

is important as it determines further management [7].

The basic evaluation includes history, physical examination, and serum hormone analysis but the clinical interpretation of these can be controversial. Thus, a widely cited study [8] asserts that a serum follicle-stimulating hormones (FSHs) level greater than 7.6 IU/L combined with a testicular long axis of 4.6 cm or less suggests that the azoospermia is due to spermatogenic dysfunction, consistent with NOA. However, another study [9] presents a subgroup of men with NOA due to uniform maturation arrest who had serum FSH less than 7.6 IU/L and normal testicular size. Similarly, the correct utility of other diagnostic modalities like genetic testing, imaging, or testicular biopsy remains a matter of debate.

Professional and academic society guidelines for the evaluation of NOA are limited and there are many controversies in the literature. Hence, considerable di-

versity in the diagnostic approaches and management of azoospermia across the globe is to be expected.

The current study aims to assess contemporary global practices related to the diagnosis and evaluation of NOA among experts and to compare them with the current international practice guidelines and the available evidence in the literature. Expert recommendations derived through a Delphi consensus are also provided.

## **MATERIALS AND METHODS**

The global survey was approved by the Global Andrology Forum (GAF) Internal Review Board (IR-02-23-110). The checklist for Reporting Results of the Internet E-Survey (CHERRIES) was used to guide the construction, dissemination, and analysis of the questionnaire [10]. The checklist is provided in Supplement File 1.

### **1. Target population**

The survey targeted physicians who treat NOA patients in their daily practice. This group included urologists, andrologists, and reproductive endocrinologists. Clinicians not dealing with these patients were excluded.

### **2. Questionnaire creation and structure**

Members of the GAF [11], which is an online collaboration of clinicians, embryologists, and researchers interested in andrology, were invited to submit multiple-choice questions on relevant clinical aspects of the evaluation and management of NOA. These suggestions were extensively reviewed and refined, by a group of ten experienced clinicians, to reflect the different options and practices available in the diagnosis and management of patients with NOA. The option “not applicable” was added when respondents did not encounter a particular situation in their clinical practice. The final survey had 56 questions accompanied by an invitation letter that mentioned the aims of the survey and recorded the respondent's consent to participation (Supplement File 2). While completing the survey, respondents were able to scan, review, and edit their responses before the final submission. This paper discusses the first part of the survey covering section 1 on demographic data (Q1–8) and section 2 on diagnosis and evaluation (Q9–21).

### **3. Questionnaire dissemination**

The questionnaire was created using Google Forms and was available online from July 21st, 2022, to September 9th, 2022. The survey was published on the website of the GAF and all members were invited to complete the survey if they fit the inclusion criteria. On the final page, the respondents were able to recommend other experts who met the inclusion criteria. The survey questionnaire was also distributed to the members of the different organizations listed under the Acknowledgment.

### **4. Data collection and analysis**

The survey data were extracted as a CSV file from the survey platform. Blank and duplicate responses were excluded. Partial responses were accepted if they included some questions beyond demographics. MedCalc® (MedCalc Software Ltd) was used to calculate responses and generate tables and graphs. When a question allowed more than one response, the total number of responses was used for calculations. Some respondents skipped some questions and hence the total number of responses per question varied.

### **5. Society guidelines**

The male infertility guidelines of the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) [12], the European Association of Urology (EAU) [13] and the European Academy of Andrology (EAA) [14,15] were reviewed for their recommendations on the evaluation and diagnosis of NOA.

### **6. GAF expert recommendations**

GAF expert recommendations were formulated using a Delphi process. Two senior authors (RS, AR) formulated the statements based on the survey results, available professional society guidelines, and the latest literature on the subject (Supplement File 3). These were then forwarded to 43 GAF clinicians with at least 15 years of experience in treating NOA. They rated the recommendations on a scale from 1 to 10, 1 being “completely disagree” and 10 “completely agree.” When they disagreed with the statement, they were asked to provide a new changed recommendation. The final recommendation was accepted once 70% of the respondents scored 7 or above.

## RESULTS AND DISCUSSION

In the current paper, we present the results of the first 21 questions dealing with the demographics of the survey and the approach to the evaluation of NOA.

The results of the survey have been grouped based on the question topics. For each group of questions, the survey results are discussed in the context of the guideline recommendations from major male infertility societies (AUA/ASRM, EAU, and EAA) and an exten-

sive literature review of relevant contemporary publications. Finally, these are summarized as expert recommendations based on the Delphi process described above. All recommendations were accepted in the first round of the Delphi process (Table 1).

### 1. Demographics

A total of 367 participants from 49 countries submitted their answers. Of these, 31 responses were excluded, either due to incomplete data (n=6) or submission by

**Table 1.** Comparison of the different guidelines on NOA

|   | AUA/ASRM   | EAU   | EAA  |
|---|--|---|--|
| Incidence of NOA                                  | Not mentioned  | Obstructive azoospermia is less common than NOA and occurs in 20%–40% of men with azoospermia   | Not mentioned                                |
| Presence of varicocele in NOA                     | Not mentioned  | 10.9% of men with azoospermia have varicocele   | Not mentioned                                |
| Number of semen samples before the diagnosis      | 2  | 2   | Not mentioned                                |
| Optimal time interval to repeat semen analysis    | 1–2 weeks  | No specific recommendation  | Not mentioned                                |
| Initial hormonal evaluation                       | Total testosterone and FSH   | Total testosterone and FSH/LH   | No specific recommendation                   |
| Genetic testing                                   | Karyotype and YCMD for men with azoospermia  | Karyotype analysis and YCMD<br>Gene coding for <i>CFTR</i> to exclude concomitant mutations   | Karyotype analysis for detecting KS and YCMD |
| Genetic counselling                               | No specific recommendation   | Mandatory in couples with genetic abnormalities prior to any ART protocols<br>For all men with azoospermia<br>For all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease | Mandatory for all men with YCMD              |
| Modalities to differentiate OA and NOA            | History, physical examination (small volume testes), semen volume, and hormonal status (FSH, LH, testosterone)   | No specific recommendation  | No specific recommendation                   |
| Diagnostic testicular biopsy                      | Should not be routinely performed to differentiate between OA and NOA<br>May be considered in infertile men with normal semen volume, normal testicular volume, and FSH<7.6 and no signs of epididymal engorgement | Performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate  | No specific recommendation                   |
| Predictors of successful surgical sperm retrieval | No specific recommendation   | No preoperative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA   | No specific recommendation                   |

AUA: American Urological Association, ASRM: American Society for Reproductive Medicine, EAU: European Association of Urology, EAA: European Academy of Andrology, NOA: non-obstructive azoospermia, FSH: follicle-stimulating hormone, LH: luteinizing hormone, KS: Klinefelter syndrome, YCMD: Y chromosome microdeletion, OA: obstructive azoospermia, ART: assisted reproductive technology, CFTR: cystic fibrosis transmembrane conductance regulator.



an ineligible respondent (n=25). Thus, a total of 336 participants were included in the study. The highest responses were received from respondents from Italy (n=36, 10.7%), Turkey (n=35, 10.4%), and India (n=35, 10.4%). Respondents and countries are presented in Fig. 1.

The majority of respondents were attending physicians, with training in general urology or andrology, and were equally divided between academic and private practice (Table 2). Almost half of the survey participants had 11 or more years of experience (Fig. 2) with more than 30% evaluating 11–20 new infertile men per week (Fig. 3).

## 2. Diagnosis and evaluation of NOA

### 1) Incidence of NOA in men presenting with infertility

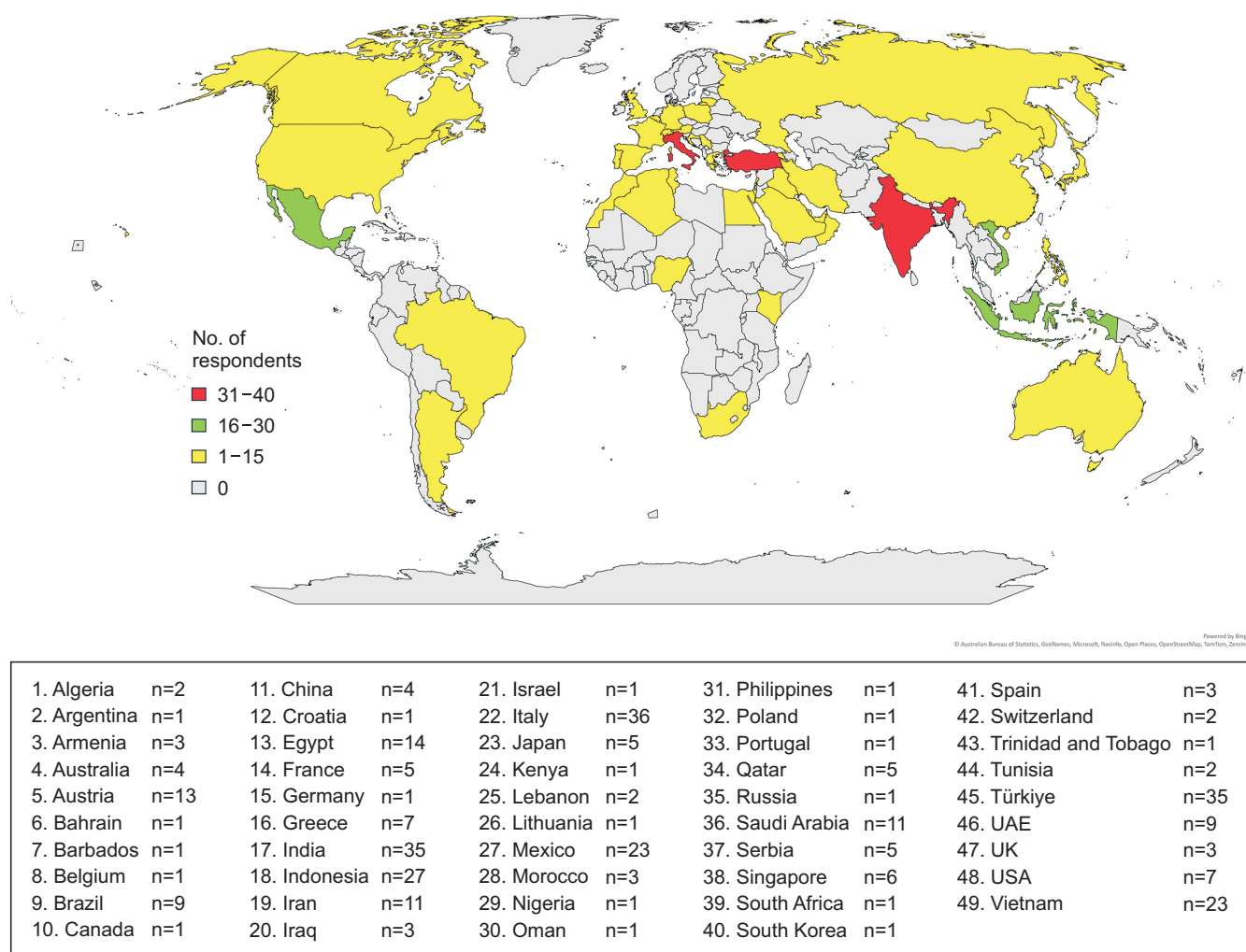
#### (1) Survey results

NOA appears to be a common problem in male infertility clinics with 39.6% of respondents reporting that 10%–25% of the infertile men they see present with NOA, and 19.94% reporting that >25% of their infertile men had NOA (Fig. 4).

Almost two-thirds (62.4%) of the respondents reported that at least 10% or more of their patients with NOA had a clinically significant varicocele (Fig. 5).

#### (2) Guidelines

Neither ASRM/ASRM nor EAA guidelines men-

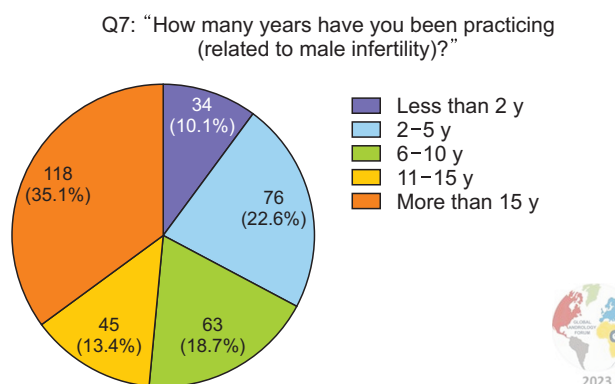


**Fig. 1.** Geographical distribution of respondents. The number of respondents is shown in brackets after the name of each country, while the numbers on the map indicate the ranking of the countries according to the number of respondents. The map is also color-coded according to the number of respondents in each country.

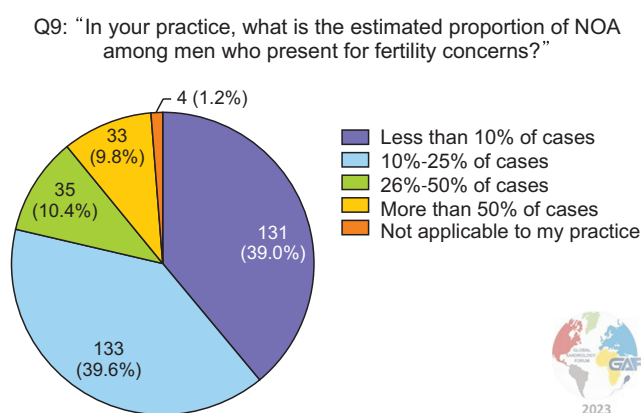
**Table 2.** Demographic characteristics of the respondents

|  | Number (%)  |
|--|-------------|
| Q4: What is the nature of your employment?                                   |             |
| Physician, attending or fellow   | 281 (83.63) |
| Physician, resident  | 37 (11.01)  |
| Advanced practice provider (Physician Assistant, Nurse Practitioner)         | 7 (2.08)    |
| Others   | 11 (3.27)   |
| Q5: What is your area of specialization (as it relates to male infertility)? |             |
| Fellowship-trained reproductive urology                                      | 99 (29.46)  |
| General urology  | 115 (34.22) |
| Reproductive Endocrinology/ART specialist                                    | 67 (19.94)  |
| Endocrinology  | 11 (3.27)   |
| Other (specify)  | 44 (13.09)  |
| Q6: What is your practice setting?   |             |
| Academic   | 85 (25.29)  |
| Public   | 39 (11.60)  |
| Private  | 102 (30.35) |
| Multiple   | 108 (32.14) |
| Other (specify)  | 2 (5.95)    |

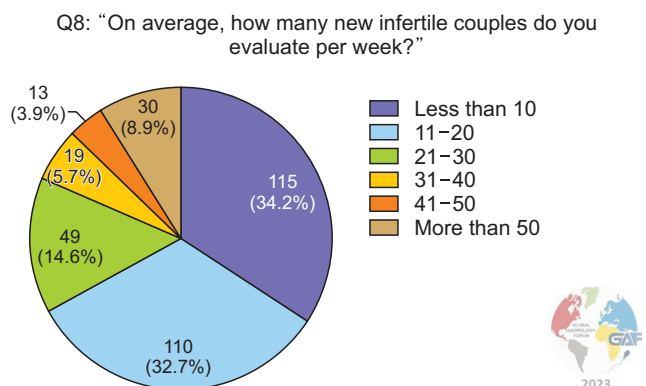
ART: assisted reproductive technology.



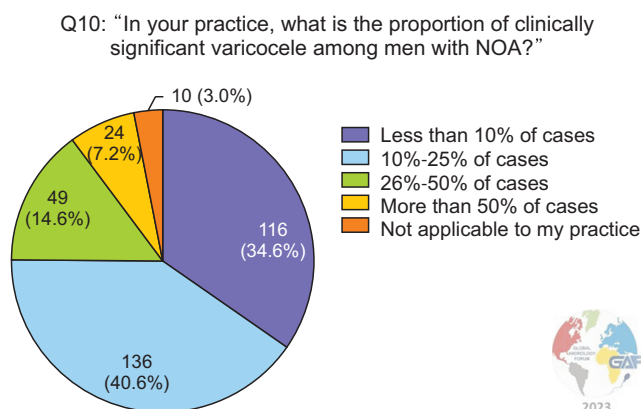
**Fig. 2.** The number of years the respondents have been practicing.



**Fig. 4.** Estimated proportion of NOA in men presenting with infertility. NOA: non-obstructive azoospermia.



**Fig. 3.** The average number of new infertile couples evaluated per week by the respondents.



**Fig. 5.** Proportion of clinically significant varicocele among men with NOA. NOA: non-obstructive azoospermia.

tion the estimated prevalence of NOA among infertile men. In the EAU guidelines, the estimated proportion of azoospermia among men who present for fertility evaluations is 11.2% [13]. Although there is no explicit proportion of NOA in the EAU guidelines, it is stated that the prevalence of OA is less frequent compared to NOA at one-fifth to two-fifths of men with azoospermia. Therefore, the proportion of NOA is around 60% to 80% of men with azoospermia. EAU guidelines mentioned that the proportion of varicocele among men with azoospermia is 10.9%, however, no specific proportion is stated for NOA. On the other hand, both AUA/ASRM and EAA guidelines do not mention any specific proportion for this group [12,14,15].

### (3) Discussion

This survey shows that NOA is commonly encountered in specialized infertility clinics around the globe. The majority of cases of NOA are due to primary hypogonadism (hypergonadotropic hypogonadism or testicular failure), while NOA due to secondary hypogonadism (hypogonadotropic hypogonadism) is uncommon [7]. There is a wide range of congenital, environmental, iatrogenic, and acquired conditions that can cause testicular failure leading to NOA [16].

While varicocele is commonly associated with oligoasthenozoospermia with an estimated prevalence of 35% [17], it is uncommon for it to be the primary cause of azoospermia. However, 5% to 10% of men with NOA have been reported to have an associated clinical varicocele [18], although in the current survey a higher incidence is suggested.

### (4) Expert recommendation

The majority of cases of azoospermia are non-obstructive and are due to primary testicular failure. The clinical relevance of a varicocele associated with NOA is unclear.

## 2) Number of semen samples to confirm the diagnosis of NOA

### (1) Survey result

Of 334 respondents, more than 80% requested two semen analyses before diagnosing NOA. Forty-six participants (13.8%) chose the “3 or more” option, whereas only 11 participants (3.3%) requested just one semen sample to diagnose NOA (Fig. 6).

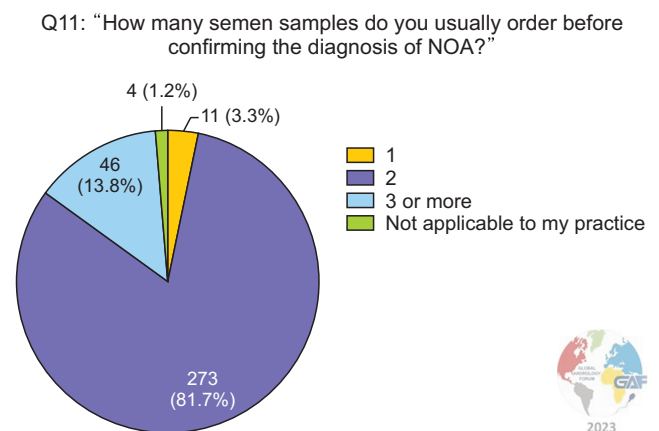
### (2) Guidelines

Although there is no specific mention in the EAA guidelines, both the AUA (statement 11) and EAU (11.6.1.2.3) guidelines state that a second semen sample is mandatory if the initial semen analysis shows azoospermia [12,13].

### (3) Discussion

The practice of the majority of the respondents is in line with the guidelines' recommendation of requesting a second semen sample if the initial examination showed an absence of sperm in the ejaculate. However, about 14% of the participants recommend 3 or more tests to arrive at the definitive diagnosis, possibly reflecting the finding that some men with NOA do occasionally have sperm in the ejaculate which may be detected only on repeated testing [19,20]. Thus, Schlegel et al [21,22] recommended a semen analysis on the day before the planned sperm retrieval procedure.

The method of examination of the semen sample can also impact the diagnosis of azoospermia. Centrifugation of the semen sample at 3,000 g for 15 minutes and examination of the pellet at 200× magnification (EUA guideline 11.3.2) or at 400× magnification (EUA guideline 11.6.1.2.3) [13] is recommended to confirm the diagnosis of azoospermia. The whole pellet should be thoroughly examined; a study using an extended sperm preparation found sperm in 35% of men who were initially diagnosed with NOA, thus preventing them from undergoing unnecessary sperm retrieval [23]. In another study, the use of nuclear fast picroindigocarmine (NF-PIC) staining in combination with Cytospin cen-



**Fig. 6.** Number of semen samples usually ordered prior to confirming a diagnoses of NOA. NOA: non-obstructive azoospermia.

trifugation found sperm in 23.9% of samples deemed azoospermic by conventional examination [24].

#### (4) Expert recommendation

Due to possible fluctuations, one semen sample might not be enough to diagnose azoospermia. At least two separate semen samples should be examined, after centrifugation to create a pellet, to establish a diagnosis of azoospermia.

### 3) Optimal time interval to repeat semen analysis in diagnosing NOA

#### (1) Survey result

Half the respondents (49.4%) do the second semen test within two to four weeks of the first test, while one-fourth (22.9%) prefer to wait for 3 months (Fig. 7). However, 10.1% of respondents highlighted that the interval between tests is best optimized as per the individual case.

#### (2) Guidelines

According to the AUA/ASRM guidelines, in cases of azoospermia a confirmatory semen analysis should be obtained at least one to two weeks later (AUA guideline statement 11) [12]. There is no specific recommendation in terms of the optimal time to repeat semen testing in EAA or EAU guidelines [13-15].

#### (3) Discussion

There is currently no study that definitively identifies the ideal time interval between two semen analyses for diagnosing NOA since azoospermia is typically used as an exclusion criterion in research that examines the ideal time for semen analysis [25,26]. Thus,

while the AUA/ASRM guidelines recommend repeating the semen analysis after a couple of weeks, it is important to bear in mind that after exposure to reversible causes of azoospermia like high fever, infection, major medical illness, exposure to toxins, chemotherapy or radiotherapy, or some medications, the reappearance of sperm in ejaculate may take several weeks to months [27-33].

While the majority of participants of the survey cited a period of 14 to 29 days as ideal for the interval between two semen analyses, 22.9% cited a period of three months. The adoption of a three-month time-frame seems reasonable conceptually as it represents a full cycle of spermatogenesis [34]. Only 9.2% of participants routinely repeat the semen analysis in less than 14 days. However, individual considerations like the couple's age, urgency for planning the next step, and the logistics for repeating the semen test may also influence the timing of the next test.

#### (4) Expert recommendation

Generally, at least a month's interval is preferable between two semen reports in an azoospermic man, but the physician's clinical judgment should be used to determine the duration between the two tests, depending on individual circumstances and history of any recent medical illness that could have affected spermatogenesis.

### 4) Hormonal evaluation

#### (1) Survey result

The majority of respondents routinely perform serum FSH, luteinizing hormone (LH), and total testosterone tests in patients with NOA, and around half of the respondents also check for serum prolactin and estradiol levels. Only 15.5% consider inhibin-B levels to be of value (Fig. 8).

#### (2) Guidelines

The AUA/ASRM guidelines recommend an initial assessment of serum total testosterone and FSH levels; if the testosterone level is <300 ng/dL then they recommend repeating the total testosterone assay together with the measurement of free or bioavailable testosterone, serum LH, prolactin and estradiol (Statement 10). EAU guidelines recommend the measurement of serum total testosterone with FSH and LH (Guideline 11.3.4) [12,13]. The AUA guidelines do not discuss inhibin-B

Q12: "How long do you think is the optimal time interval to repeat sperm analysis in diagnosing NOA?"

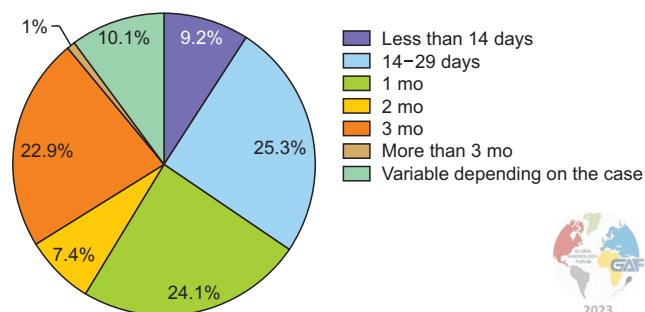
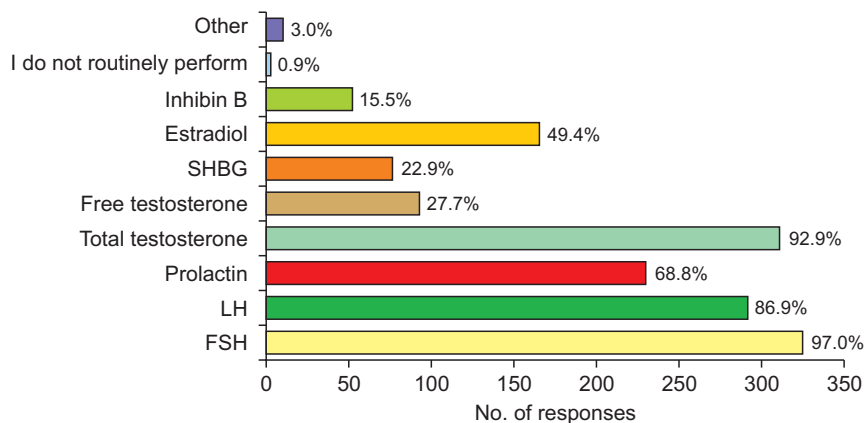


Fig. 7. Optimal time to repeat sperm analysis in diagnosing NOA. NOA: non-obstructive azoospermia.



Q13: "What hormonal evaluation do you routinely perform in patients with NOA?"



**Fig. 8.** Hormonal evaluation routinely performed for patients with NOA. NOA: non-obstructive azoospermia, SHBG: sex-hormone binding globulin.

while the EAU guidelines state that though inhibin-B is a useful indicator of Sertoli cell function, its diagnostic utility is not superior to FSH and hence is not widely used (Guideline 11.6.1.2.4). The EAA guidelines do not provide specific recommendations for hormonal evaluation for men with NOA [14,15].

### (3) Discussion

The hypothalamic-pituitary-gonadal axis is essential for spermatogenesis. Rapid pulses of gonadotropin releasing hormone (GnRH) stimulate the release of FSH and LH from the anterior pituitary gland. FSH acts on the testes to promote spermatogenesis via Sertoli cells, whereas LH stimulates the Leydig cells to produce testosterone [35]. Studies have shown that serum FSH, LH, and testosterone levels are significantly different among men with NOA compared to those with OA [36,37].

The value of serum total testosterone level may not represent the functional testosterone available due to the changes in serum sex-hormone binding globulin (SHBG) levels which may be altered due to metabolic syndrome, hypo/hyperthyroidism, pituitary disease, chronic liver disease, prostate cancer, nephrotic syndrome, estrogen use, as well as drugs such as some anticonvulsants and steroids [38,39]. Therefore, the calculation of free testosterone may be useful in borderline cases [38].

Sertoli cells produce inhibin-B to give negative feedback. Estradiol is the predominant form of estrogen that mediates the negative feedback to the hypothala-

mus thus impacting GnRH release and consequently regulating spermatogenesis. Serum estradiol levels in infertile men with NOA may vary but the majority (up to 71.1%) have normal levels [40]. Thus, estradiol should be assessed for selected patients such as those with obesity, those working in a polluted workplace, or before trying hormonal therapy [40].

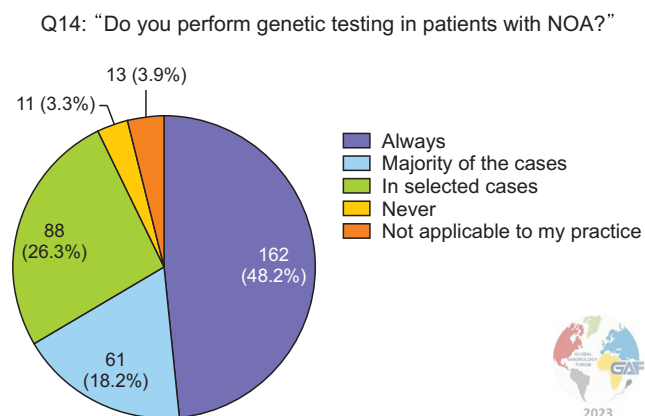
An elevated level of prolactin can also result in negative feedback to pituitary gonadotrophin secretion by directly influencing the prolactin reception in the testis, which then results in detrimental effects on spermatogenesis [35,41]. A study by Gonzales et al [42] reported a significantly higher prolactin level among the azoospermic group compared to the normozoospermic group while another study found that up to one-fourth of men with azoospermia have hyperprolactinemia [43]. However, there is no established causation or clinical relevance of raised prolactin to azoospermia. In a study of 204 men attending infertility clinics, there was no significant difference in pregnancy rates between men with high (greater than 5 ng/mL) and low (less than or equal to 5 ng/mL) prolactin [44]. Therefore, it is suggested that the investigation for prolactin in an azoospermic male is done only for those with hypogonadotropic hypogonadism, or with concomitant complaints of sexual dysfunction (especially decreased libido), or if there are clinical symptoms of hyperprolactinemia or pituitary disease [45].

The result of the survey showed that serum FSH, LH, and total testosterone were the most common initial hormones evaluated in patients with NOA. This

corresponds with the guidelines' recommendations.

#### (4) Expert recommendation

The initial evaluation of a patient with suspected NOA should include serum total testosterone level, FSH, and LH, as these hormones are the primary regulator for spermatogenesis. When the serum total testosterone level does not match the clinical symptoms or if there is any condition that could dramatically alter the SHBG level, then the calculation of free testosterone (after SHBG assay) is recommended. Serum estradiol should be measured in obese men. Serum prolactin should be assayed if there is an associated decreased sexual desire and erectile dysfunction.



**Fig. 9.** Proportion of respondents who perform genetic testing in patients with NOA. NOA: non-obstructive azoospermia.

## 5) Genetic testing

### (1) Survey result

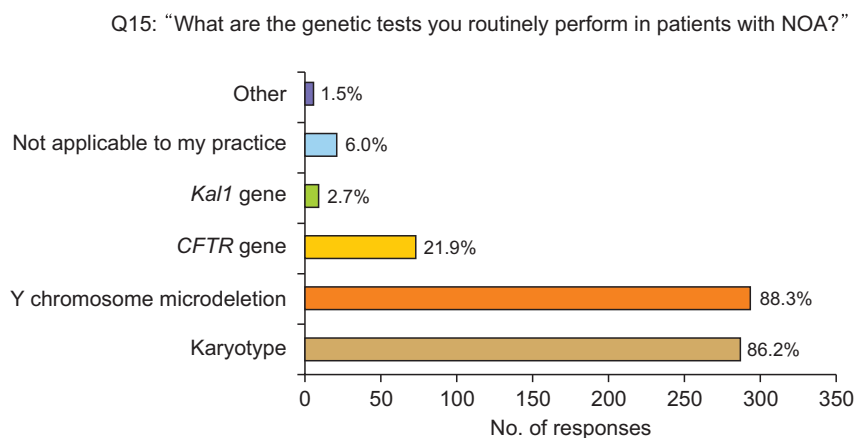
Out of 335 respondents, two-thirds ask for genetic testing in men with NOA in all or the majority of the cases, while 26.3% of them would offer it in selected cases. A small minority (3.3%) of the participants chose the "never" option (Fig. 9).

For the genetic tests that are routinely performed, the majority of respondents order karyotype analysis and Y chromosome microdeletion, while one-fifth of respondents also test for the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in patients with NOA. Only a few of the respondents (2.7%) ask for *Kal1* gene test (Fig. 10). For genetic counseling, half of the respondents refer their patients to a genetic counselor, while 22.1% feel that they could counsel adequately by themselves (Fig. 11).

### (2) Guidelines

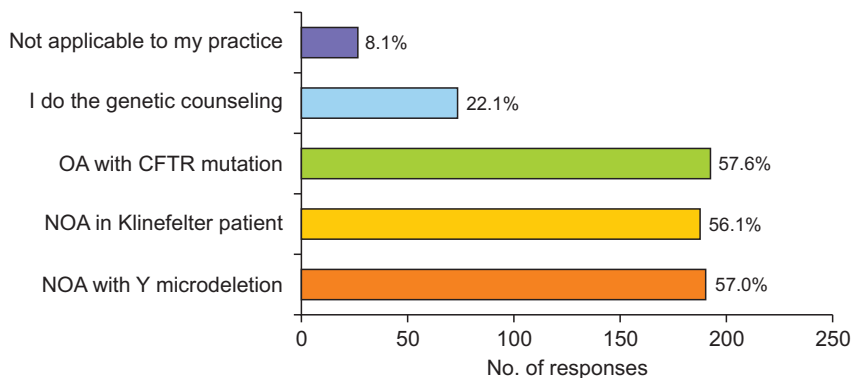
All guidelines agree on the need for karyotype and Yq deletion screening in all men with NOA [12-15]. The EUA guidelines also recommend testing for concomitant *CFTR* mutations (Guideline 11.6.2.1) [13].

The EAU guidelines recommend offering genetic counseling to men with azoospermia and oligozoospermia (spermatozoa <10 million/mL), especially for those who have a potential for inheritable disease and before any assisted reproductive technique (ART) procedure. In congruence, the EAA guidelines recommend offering genetic counseling for men with Y chromosome microdeletion and selected cases of men with Klinefelter Syndrome [14,15].



**Fig. 10.** Routinely performed genetic tests in patients with NOA. NOA: non-obstructive azoospermia, *CFTR*: cystic fibrosis transmembrane conductance regulator.

Q21: "In which situation do you refer an azoospermic patient to a genetic counselor"



**Fig. 11.** Conditions in which the respondents refer an azoospermic patient to a genetic counselor. NOA: non-obstructive azoospermia, OA: obstructive azoospermia, CFTR: cystic fibrosis transmembrane conductance regulator.



### (3) Discussion

A male patient with azoospermia or severe oligospermia has a higher likelihood of having genetic abnormalities. A study of 291 men attending infertility clinics reported that chromosomal abnormalities were significantly higher among azoospermic men (35.0%) compared to patients with normozoospermia (1.1%) [46]. Another study of 1,663 infertile men with azoospermia showed that the rate of chromosomal abnormalities was around 14.4% [47]. Among these abnormalities, Klinefelter syndrome was detected in 64% to 73% of patients [46,47], followed by autosomal abnormalities, terminal deletion of chromosomal Y, and XYY karyotypes [46]. Another study of 765 infertile men with NOA, showed that 13.99% had Y chromosome microdeletions [48].

These studies highlight the need for karyotyping and Y chromosome microdeletion testing in patients with NOA, which is consistent with the guidelines and practices of the majority of our respondents.

On the other hand, 2.7% of respondents would order *Kal1* gene testing. *Kal1* is the first gene discovered in X-linked Kallman Syndrome patients [49] and is the most common cause of congenital hypogonadotropic hypogonadism especially when associated with anosmia or severe hyposmia [5]. The test of *Kal1* should be reserved for those with clinical suspicion of Kallman Syndrome.

There are many other genes as well as mutations of genes that are proposed to be responsible for NOA [50], but several of them have not yet been confirmed or are

so rare in the community that routine screening would not be cost-effective [51].

Interestingly, 21.9% of participants stated that they routinely perform *CFTR* gene mutation testing in patients with NOA although *CFTR* gene mutation does not cause NOA, and testing for *CFTR* mutations is causally indicated in OA with congenital seminal tract anomalies. A reason to do this test could be linked to the high prevalence of *CFTR* mutations in some geographical areas and in these populations, both partners of a couple undergoing ART for NOA may coincidentally also be carriers of *CFTR* mutations. If that is found to be the case, then preimplantation genetic testing would be required to avoid cystic fibrosis in the offspring.

A causative role of *CFTR* mutations in NOA is unlikely. A case-controlled study of 100 men with NOA found that certain polyvariant mutations of the *CFTR* gene (T5 allele and TG12-T5-V470 genotypes) were associated with a higher risk of NOA, though the common F508del and R117H mutations were not found [52]. A study of 100 Iranian infertile men with NOA also showed that neither  $\Delta I507$  nor  $\Delta F508$  *CFTR* gene mutations played a role [53].

Genetic counseling is an important aspect of the management of azoospermia [54]. It includes a discussion of the risk and clinical consequences of vertical transmission to the offspring, and whether preimplantation genetic testing is advisable [55]. Our survey shows that a significant proportion of clinicians offer counseling themselves and do not refer the couple to a genetic counselor. This finding highlights the need for

providing training in genetic counseling to clinicians.

#### (4) Expert recommendation

Karyotype and Y microdeletion tests should be recommended for NOA patients, while *CFTR* gene mutation tests should be done only in cases of vas aplasia or congenital obstruction, or in regions with a high prevalence of carriers for *CFTR* mutations. Currently, other genetic tests like full exome or genome screening are not recommended as routine tests.

### 6) Preferred modalities to differentiate OA and NOA

#### (1) Survey result

Almost half (45.1%) of the respondents do not perform diagnostic testicular biopsy to differentiate between OA and NOA, while one-third (34.6%) perform

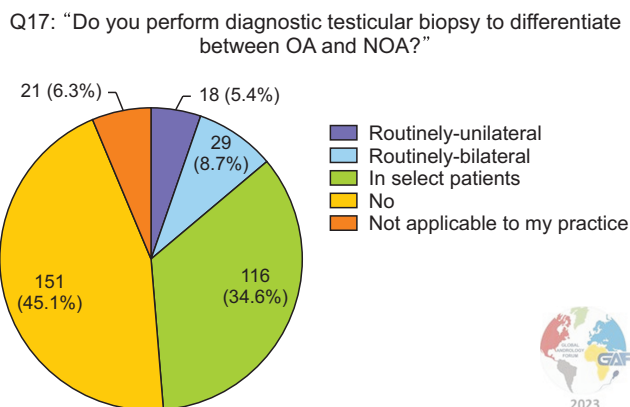
it in selected cases. However, 14.1% of respondents reported that they routinely perform either unilateral or bilateral diagnostic testicular biopsies (Fig. 12).

In order to differentiate between NOA and OA, most respondents rely on clinical examination (76.1%), serum levels of reproductive hormones (69.6%), and basic and extended semen tests (68.1%). Only a minority of clinicians (29.0%) consider scrotal ultrasonography as being helpful in distinguishing between OA and NOA (Fig. 13).

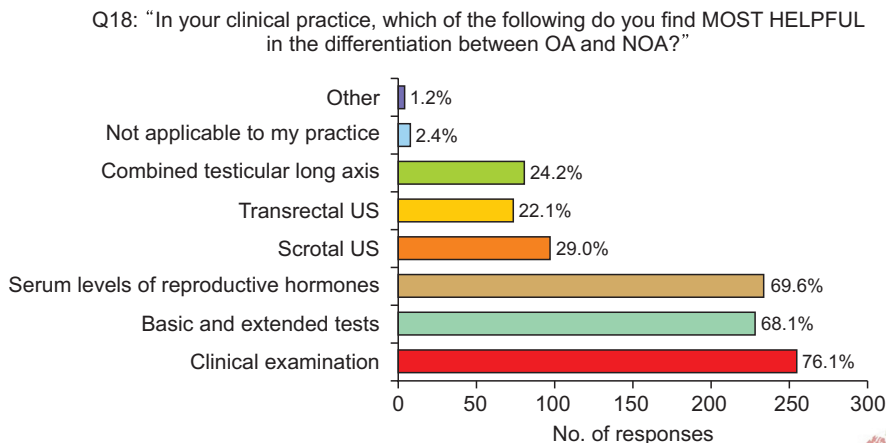
#### (2) Guidelines

The EAU guidelines state that testicular histopathology from a diagnostic testicular biopsy is an important predictor of spermatogenesis and sperm retrieval, but it should not be performed in isolation and should, instead, always be combined with therapeutic sperm retrieval (Guideline 11.6.1.2.6). Further, the EAU guidelines state that diagnostic fine needle aspiration should not be performed in isolation without simultaneous therapeutic testicular sperm extraction (TESE) [13].

Likewise, the AUA/ASRM states that in the majority of cases, clinical and laboratory results are sufficient to differentiate NOA or OA without the need for an invasive diagnostic biopsy procedure (Guideline statement 11). Azoospermic men with small testicular volume, elevated serum FSH, and normal semen volume typically belong to the NOA group, while those with normal testis volume (length >4.6 cm) and serum FSH level <7.6 IU/mL will most likely have OA. The diagnosis of OA is more convincing if there is engorgement of proximal epididymis or clinical absence of



**Fig. 12.** Most helpful modality to differentiate between OA and NOA. NOA: non-obstructive azoospermia, OA: obstructive azoospermia.



**Fig. 13.** Diagnostic testicular biopsy to differentiate between OA and NOA. NOA: non-obstructive azoospermia, OA: obstructive azoospermia.



vasa deferentia. A diagnostic testicular biopsy may be infrequently indicated in case of “intermediate values” and should be combined with sperm cryopreservation (Guideline statement 20) [12].

The EAU guidelines do not make any recommendation for an US in the evaluation of NOA, but an earlier section (11.3.6.1) discusses that an US may help in identifying testicular dysgenesis or testicular tumors, and in assessing testicular volume [13]. Both the AUA (Guideline statement 22) and EAU (11.3.6.2) suggest that trans-rectal sonography should be limited to cases where there is suspicion of distal obstruction at the level of the ejaculatory ducts, and need not be done routinely in all cases [12,13]. There is no specific mention in the EAA guidelines regarding modalities to differentiate between OA and NOA [14,15].

### (3) Discussion

Categorization of azoospermia into OA or NOA is critical as the management strategies for the two are very different. While testicular biopsy is the “gold standard” to discriminate OA from NOA, it is an invasive procedure and should be reserved for inconclusive cases such as patients with normal FSH, normal testicular size, and no sign of obstruction [56]. In the majority of cases, differentiation can be made through clinical, biochemical, genetic and imaging assessment [56].

In our survey, almost half (45.1%, n=151) of the participants do not perform diagnostic testicular biopsy to differentiate between OA and NOA, while 34.6% of them would perform it in selected cases. This finding is consistent with the literature as well as the guidelines.

The AUA guidelines differentiate between OA and NOA based on FSH and testicular size (long axis). These are derived from a study by Schoor et al [8] which showed the serum FSH level was 7.6 mIU/mL or less and the testicular long axis was 4.6 cm or greater in 96% of males with OA. On the other hand, serum FSH levels higher than 7.6 mIU/mL and a testicular long axis less than 4.6 cm were present in 89% of males with NOA. While this is a useful finding for differentiating between OA and NOA, it has many limitations. In the study, 21.6% of men with OA had a long axis <4.6 cm and 22.2% of men with NOA had a long axis >4.6 cm. Similarly, 9.3% of men with OA had FSH >7.6 mIU/mL while 24.1% of men with NOA had FSH <7.6 mIU/mL. Hence, it is not uncommon to have men with

large testes and normal FSH who have NOA. Thus, a 2007 study from Schlegel's group found that 32 men from a study group of 150 had maturation arrest but normal FSH and normal testicular size [9]. Hence, in addition to the testes size and FSH level, the turgidity of the epididymis on clinical examination should be considered [12]. This is in line with the survey finding where “clinical examination” was reported as “most helpful” in differentiating between OA and NOA.

We also need to consider that the range of normal FSH values vary widely from laboratory to laboratory [12]. In the study by Schoor et al [8], the upper limit of normal FSH was 15 mIU/mL. Thus, the value of 7.6 mIU/mL lies in the lower half of the normal range, and hence the cut-off value for FSH may be better defined as a value in the lower half of the range for that laboratory rather than as an absolute value.

Other studies have suggested different parameters to distinguish between OA and NOA. A study by Shamohammadi et al [37] proposed a cut-off of serum FSH >8.9 mIU/mL and testicular long axis <39 mm; their positive predictive value for NOA was 97.02% and for OA was 78.8%. Differences in cut-off point may also result from ethnic differences with Asian males reported to have higher serum FSH and smaller testes compared to Caucasian men [57,58].

Ultrasonography has a limited role in differentiating between OA and NOA and may be more relevant for ruling out a testicular tumor before therapeutic TESE.

### (4) Expert recommendation

In most cases clinical and laboratory results are sufficient to diagnose NOA or OA.

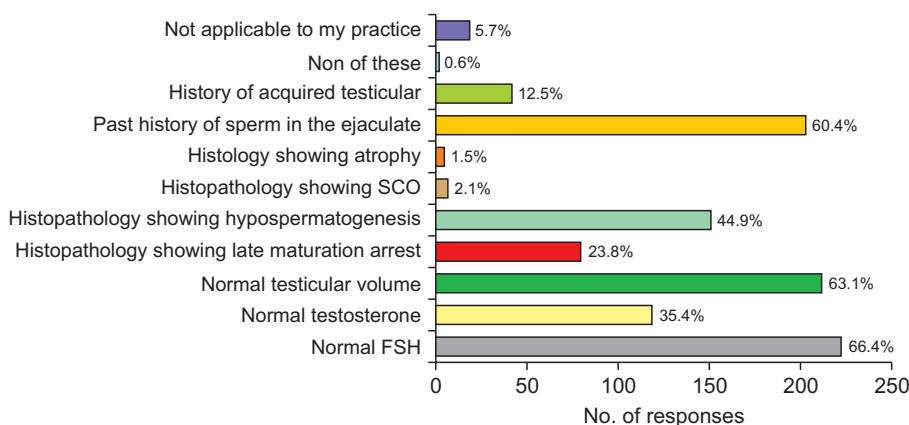
Diagnostic testicular biopsy before definitive TESE is not recommended for use in routine clinical practice. Only in some cases, where the serum FSH and LH, and the testicular volumes are normal, a testicular biopsy may be indicated to provide a definitive diagnosis, and should always be combined with therapeutic TESE.

## 7) Predictive factors of sperm retrieval by cTESE/ mTESE

### (1) Survey result

The majority of respondents (66.4%) stated that normal serum FSH predicts a higher chance of sperm retrieval by cTESE (conventional TESE) or by mTESE (microdissection TESE). Normal testicular volume (63.1%) and a history of sperm (60.4%) in the ejaculate

Q20: "In your practice which of the following is/are predictive of a higher chance of sperm retrieval by cTESE/mTESE?"



**Fig. 14.** Predictive factors of a higher success rate of sperm retrieval by cTESE/mTESE. cTESE: conventional therapeutic testicular sperm extraction, mTESE: microdissection therapeutic testicular sperm extraction, FSH: follicle-stimulating hormone, SCO: Sertoli cell only.

were the other popular answers (Fig. 14).

## (2) Guidelines

The EAU guidelines state that testicular histology is a good predictor of successful surgical sperm retrieval but do not recommend routinely doing a biopsy for this purpose. They further state that serum hormone levels of FSH, LH, Inhibin, and anti-Mullerian hormone (AMH) have variably correlated with sperm retrieval in various studies and, given the conflicting results, none may be considered a reliable predictor of sperm presence in NOA (Guideline 11.6.2.3) [13].

The AUA/ASRM and EAA guidelines do not mention any specific factors for predicting sperm retrieval in NOA [12,14,15].

## (3) Discussion

Predictors of successful TESE in patients with NOA have been widely studied but without consensus. Assessing the role of FSH, a single-center retrospective study of 108 patients with NOA showed that lower serum FSH and higher patient age (mean age of  $40.04 \pm 12.22$  years *versus*  $33.98 \pm 6.18$  years) were independent predictors of successful sperm retrieval in mTESE [59]. Other studies reported that testicular volume, FSH, and inhibin level were correlated with cTESE outcome [60]. Similarly, a new systematic review also showed that FSH has an inverse relationship to sperm retrieval for mTESE and cTESE and can be the sole predictor of cTESE success [61]. A recent meta-analysis reported

that in men with Klinefelter's syndrome, younger age and higher testosterone were favorable indicators for successful sperm retrieval by mTESE, but found that no factor could predict recovery in men with AZFc microdeletions [62]. However, on the other hand, in a study on 329 Japanese men with NOA, Enatsu et al [63] did not find a significant correlation between testicular volume, FSH, LH, or testosterone and sperm retrieval by mTESE. Instead, older age and non-idiopathic etiology were significant in predicting sperm retrieval. Also validating the predictive value of the etiology of NOA, a systematic review and meta-analysis of 13 retrospective cohort studies comparing men with idiopathic NOA and those with surgically treated cryptorchidism, found that the sperm retrieval rates (SRR) were significantly higher in men with cryptorchidism who underwent orchiopexy than in men with idiopathic NOA (71.2% *vs.* 38.4%, relative risk [RR]=1.90; 95% confidence interval [CI]: 1.40–2.58;  $p < 0.0001$ ) [64]. Moreover, the SRR was significantly higher in men who underwent orchiopexy before the age of 10 years than in those who had surgery at an older age (RR=1.25, 95% CI: 1.06–1.47).

Several studies have found testicular histology to be the most accurate single factor in predicting TESE success [65,66]. A recent multi-center study has suggested that serum AMH levels  $< 4$  ng/mL was associated with a higher chance of finding sperm in men with NOA [67].

However, there is no single factor that can precisely predict the success of TESE [68] and some authors have

tried to build a predictive model for successful sperm retrieval in both cTESE and mTESE using multiple parameters [60,69,70].

#### (4) Expert recommendation

There are no preoperative biochemical or clinical variables that definitively predict positive sperm retrieval at surgery in patients with NOA. However, normal FSH, normal testicular volume, a history of sperm in the ejaculate, and histopathology with hypospermatogenesis predict higher chances of sperm retrieval.

## CONCLUSIONS

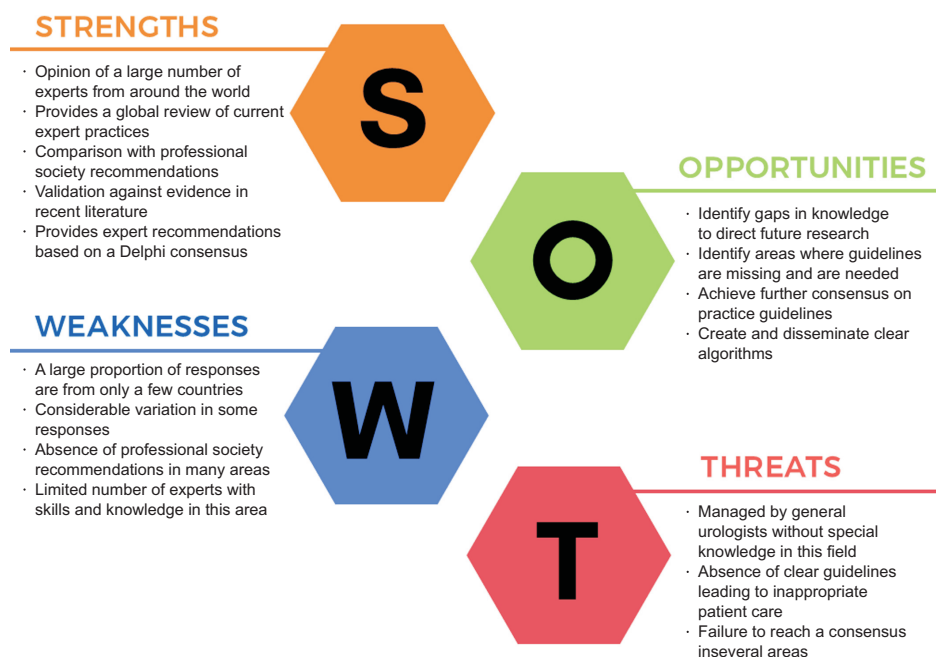
The current survey has several limitations. First, the sample population was mainly drawn from a pre-existing group of clinicians with a special interest in male infertility (GAF). This may have caused some selection bias and the sample may not be representative of male infertility clinicians in general. Second, there is a predomination of responses from some countries (Italy, Turkey, India), while there is noticeable underrepresentation from many other countries (Russia, China, Canada). Third, the total response rate of the survey could not be determined due to the multiple ways of questionnaire dissemination, including emails, direct communication, and professional society websites which resulted in an unknown total number of invitations. Fourth, subgroup analysis of results based on

specialization, practice setting, or years of practice was also limited due to small numbers in each subgroup.

However, despite these limitations, we believe that the 336 responses received from 49 countries provide a valid and comprehensive perspective of global practices. As the first global survey on clinical practices related to NOA, the present survey provides important information on real-life practices. A SWOT (Strength, Weakness, Opportunities, Threats) analysis listing the strengths and limitations of this survey, together with opportunities for further research are summarized in Fig. 15.

Our survey on global clinical practices in the evaluation of azoospermia has shown that there is a congruity between global clinical practices, evidence in the literature, and professional society recommendations, though there are also several areas where guidelines are not available. Further, the survey shows that there is a significant proportion of clinicians whose clinical practices differ from the recommendations, which suggests the need for further training and knowledge dissemination.

In summary, most clinicians rely on at least two semen reports, done a month apart, to diagnose azoospermia. The commonly requested hormone tests for diagnosis are FSH, LH, and testosterone. Differential diagnosis between OA and NOA is based on a combination of history, physical findings, and hormone profile, though these may be misleading in men with matura-



**Fig. 15.** Strength, Weakness, Opportunities, Threats (SWOT) analysis of the survey.

tion arrest who could present with normal testicular size and normal hormone levels. Diagnostic testicular biopsy is not routinely required to differentiate between OA and NOA, and if performed in selected cases it should be combined with therapeutic TESE. Imaging does not have a major diagnostic role. Karyotype and Yq microdeletion studies are still the only genetic tests performed by the majority. There is no single test that can predict successful sperm retrieval but a combination of assessments involving FSH, testosterone, testicular size, and histology (when available) can provide a reasonable probability of outcome.

### Conflict of Interest

The authors have nothing to disclose.

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6. Egyptian Urological Association (Maged Ragab, MD, PhD)
7. Indonesian Urological Association (InaUA) and InaUA Section of Andrological Urology (Ponco Birowo, MD, PhD; Gede Wirya Kusuma Duarsa, MD, PhD; Ricky Adriansjah, MD; Widi Atmoko, MD).
8. Italian Society of Andrology and Sexual Medicine (Aldo E. Calogero, MD, Italy).

9. Italian Society of Human Reproduction (Carlo Trotta, MD, Italy; Giovanni M. Colpi, MD, Italy; Lucia Rocco, PhD, Italy).
10. Italian Society of Urology (Gian Maria Busetto, MD, PhD, Italy).
11. Lebanese Society of Urology (Mohamad Moussa, MD, Lebanon).
12. Malaysian Society of Andrology and the Study of the Aging Male (Christopher Ho, MD, Malaysia; Kay Seong, NGOO, MD, Malaysia).
13. Malaysian Urological Association (Teng Aik Ong, MD, Malaysia).
14. Mediterranean Society for Reproductive Medicine (Hassan Sallam, MD, PhD, Egypt).
15. Middle East Society for Sexual Medicine (Amr El Meliegy, MD, Egypt).
16. Moroccan Association of Andrology (AMAN) (Imad Ziouziou, MD, Morocco).
17. Nigerian Urological Association (NAUS), (Muhammad Ujudud Musa).
18. Oman Urology Society (OUS) (Mohammed S. Al-Marhoon, MD, Oman).
19. Romanian Association for Sexual Medicine (Catalina Zenoaga-Barbarosie, MSc, Romania).
20. Saudi Andrology Group (Naif Alhathal, MD, Saudi Arabia).
21. Society for Men's Health Singapore (King Chien; Joe Lee, MD, Singapore).
22. Society of Egyptian Fellows and Members of the Royal College of Obstetricians and Gynecologists (Hassan Sallam MD, PhD, Egypt).
23. Society of Urological Surgery in Turkey (SUST) (Murat Gul, MD, Turkey).
24. Turkish Society of Andrology (TSA) (Ateş Kadioğlu, MD, Turkey).
25. Turkish Association of Urology (Arif Kalkanli, MD, Turkey; Ateş Kadioğlu, MD, Turkey).
26. Vietnamese Society for Sexual Medicine (Quang Nguyen, MD, PhD; Ho Vinh Phuoc Nguyen, MD; Tan V. Le, MD; Quang Tien Long Tran, MD).

### Author Contribution

Conceptualization: RS, AR. Data curation: GMS, MG, AM.H. Methodology, Project administration: AA, DD. Writing – original draft: RS, AR, WA, MM, IZ, PK, NT, NHVP, PK, AH, GS, MG, TH, TT, PB, EK, MA, RAG, VSK, RS, GIR, GMP, EC, GMC, WZ, EP, HJP, SF, AT, CRC. Writing – review & editing: All authors.



## Supplementary Materials

Supplementary materials can be found via <https://doi.org/10.5534/wjmh.230333>.

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