ThemenCheck Medizin

Extract of HTA report

Testicular cancer

Does routine screening for men aged 16 years and older lead to better treatment outcomes?[1]

Health technology assessment commissioned by IQWiG

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[1] Translation of the publisher's comment and Chapters 1 to 10 of the HTA report HT18-01 *Hodenkrebs: Führt eine regelmäßige Früherkennungsuntersuchung für Männer ab 16 Jahren zu besseren Behandlungsergebnissen?* (Version 1.0; Status: 18 June 2020 [German original], 14 April 2021 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers.

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IQWiG coordinated the project and conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”.

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Publisher's comment

What is the background of the HTA report?

For "ThemenCheck Medizin" (Topic Check Medicine), published by the Institute for Quality and Efficiency in Health Care (IQWiG), insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies. The assessment is done in the form of a health technology assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 topics are selected each year from among all submitted proposals. According to the legal mandate, these topics ought to be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In 2018, IQWiG commissioned a team of scientists from universities in Hall in Tirol and Munich as well as from the Austrian National Public Health Institute in Vienna to investigate the selected topic HT18-01, testicular cancer screening. The team consisted of methodologists experienced in generating HTA reports, a urologist as well as experts with knowledge and experience in health economic, ethical, social, legal and organizational topics.

Why is the HTA report important?

Testicular cancer typically develops at an early age, between 25 and 45 years, and is the most common malignant neoplasm in young men. Representing 1.6% of all cancers, testicular cancer is one of the rarer types of cancer overall [2]. Testicular cancer is very treatable, and the odds of surviving the disease are great. Particularly when the disease is diagnosed at an advanced stage, however, late sequelae of cancer treatment such as nerve damage, infertility, hypertension, or peripheral neuropathy may develop [3]. If left untreated, the disease is fatal.

In Germany, men aged 45 years and older are eligible for one annual cancer screening. Statutory health insurance (SHI) benefits include, among other things, a specific anamnesis, including questions about any changes and complaints, inspection and palpation of the external genitals, palpation of the prostate as well as communication of findings with subsequent consultation [4].

Since testicular cancer typically develops before the 45th year of life, a member of the general public asked the ThemenCheck Medizin team whether it might be beneficial to start routine screening in asymptomatic men as young as 16 years of age.

For testicular cancer screening in younger asymptomatic men, 2 examinations can be distinguished: (1) regular clinical palpation and scrotal ultrasound versus (2) regular testicular self-examination (TSE) (by palpation) as instructed and encouraged by healthcare staff. While the S3 guideline "Diagnostics, therapy and follow-up of testicular germ cell tumours" advises against screening the general population for testicular cancer, it recommends that particularly younger men regularly practise TSEs since they might result in earlier diagnosis [5].

It was against this backdrop that IQWiG selected the topic "testicular cancer screening" for the generation of an HTA report. From the various perspectives of an HTA report, it was investigated whether men aged 16 years and older reap health benefits from regular clinical screening by scrotal palpation and ultrasound or regular TSEs.

Demonstrating any benefit of screening – in the form of clinical screening or TSE – would require high-quality studies to show that the advantages of screening (e.g. avoided deaths) outweigh its disadvantages (e.g. unnecessary examinations possibly followed by invasive measures).

Which questions are answered – and which are not?

The commissioned team of scientists did not find any studies investigating the benefits of testicular cancer screening. Therefore, they conclude that there is no hint of benefit or harm from routine screening – whether in the form of clinical palpation and scrotal ultrasound or TSE.

In the HTA report, the external experts further sought to answer the question of how many men in Germany might theoretically benefit from screening. The authors conclude that, due to the low incidence and good treatability of testicular cancer, only a minor potential benefit of testicular screening is theoretically expected in men aged 16 years and older. However, this minor theoretical benefit would be offset by potential harm due to unnecessary examinations possibly followed by invasive measures such as testicular exploration or removal in suspicious cases.

Given that the authors were unable to find any studies on this topic, it was not possible to draw any conclusions on the cost effectiveness of testicular cancer screening.

With regard to ethical, legal, social, and organizational aspects, the authors of the HTA report emphasize that the male general population tends to know little about testicular cancer or TSE. Studies have also shown that, where requisite information and training is provided, TSE

is practised more frequently. All things considered, however, the report concludes that general testicular cancer screening – not only in terms of benefits, but also from an ethical perspective – cannot be recommended.

These conclusions of the report apply to general testicular cancer screening in young men. A different conclusion on the benefit of screening might be reached when analysing routine screening in men with specific risk factors for testicular cancer (e.g. undescended testicle in childhood, family history or personal history of testicular cancer, infertility). In this population, the benefit of testicular cancer screening might be greater than in the general population since the probability of diseases being identified through screening is, of course, higher in high-risk groups.

In principle, men with testicular abnormalities should always promptly see a physician.

What's the next step?

The HTA report has underscored that there is no empirical or theoretical basis for recommending a population-based screening for testicular cancer in men 16 to 45 years of age. The situation might be different for men at higher risk of testicular cancer. A comment on the HTA report suggested conducting studies on this question. IQWiG welcomes this suggestion and offers constructive support for the development of relevant study concepts.

Furthermore, specific tumour markers for testicular cancer screening are currently being developed [6]. If successful, the future role of tumour markers with reliable test characteristics should be explored for testicular cancer screening in high-risk groups.

Testicular cancer is very treatable. Nevertheless, impairments can develop due to late sequelae of cancer therapy in some cases, for instance in patients starting therapy in the advanced stage of disease. The S3 guideline "Diagnostics, therapy and follow-up of testicular germ cell tumours" therefore recommends, for instance, that affected men with metastatic germ cell tumour be treated in centres with proven experience [5]. In this context, it might be worth examining whether an improvement in care might be achieved by further quality assurance measures, such as the centralized provision of services.

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HTA key statements

Research questions of the HTA report

The aims of this investigation are to

- assess the benefit of testicular cancer screening through clinical palpation and scrotal ultrasound or through testicular self-examination (TSE) in men from 16 years of age in comparison with no screening with regard to patient-relevant outcomes,
- determine the cost (intervention cost) arising from testicular cancer screening in comparison with no screening in asymptomatic men from 16 years of age,
- assess the cost-effectiveness of testicular cancer screening in comparison with no screening in asymptomatic men from 16 years of age, and
- review ethical, social, legal, and organizational aspects associated with the screening.

Conclusion of the HTA report

Due to a lack of interventional studies on benefit and harm, the question of whether routine screening of asymptomatic men from 16 years of age (at average or higher risk) results in better treatment outcomes in testicular cancer cannot be answered in an evidence-based manner. There is no hint of (greater) benefit or (greater) harm. No studies are available on cost effectiveness.

The theoretical maximum benefit indirectly derived from epidemiological studies in a supplementary presentation for the benefit assessment is relatively small in comparison with other cancers. Testicular cancer is rare, and even in the absence of routine screening, it is discovered in a relatively early stage in most cases and can be treated with correspondingly high cure rates.

Therefore, routine screening for testicular cancer in men from 16 years of age cannot be recommended at this time. This applies to both TSE and clinical palpation / scrotal ultrasound. The low potential benefit is accompanied by potential harm due to unnecessary testicular exploration or removal. Nonmalignant testicular anomalies, which are frequently discovered as a result of targeted examinations, may worry affected men and sometimes involve unnecessary resource consumption. Particularly in case of clinical examinations, it is possible for the expected harm inflicted by additional unnecessary invasive evaluations to outweigh the expected benefit when looking at the entire target population. Therefore, clinical palpation and scrotal ultrasound for screening purposes should be offered neither as a standard statutory health insurance (SHI) benefit nor as an individual out-of-pocket health

service. TSE is likely associated with less potential harm. It seems justifiable for young men worried about the risk of testicular cancer – of which there should be few according to psychosocial studies – to regularly practise TSE after they have been educated about the lack of direct evidence on their potential benefit and harm and instructed on how to perform the exam. The use of conventional health education channels to advise men to promptly see a physician for diagnostic evaluation in case of abnormalities of the testis can absolutely be recommended. Further, men should be educated about risk factors for testicular cancer and the generally more favourable benefit–harm ratio of screening for individuals at higher risk.

Given that a relatively low potential benefit is expected due to the comparatively low incidence and often relatively good treatment outlook for testicular cancer, it seems hardly advisable to overcome the lack of evidence by conducting resource-intensive interventional studies of high methodological quality in men at average risk of testicular cancer. Since the benefit of screening measures increases with the risk of developing the disease, such interventional studies should be performed in high-risk groups, if at all.

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Abbreviation	Meaning
AE	adverse events
AFP	alpha-fetoprotein
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
EBM	Einheitlicher Bewertungsmaßstab (Uniform Value Scale)
ESMO	European Society for Medical Oncology
EUnetHTA	European network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOÄ	Gebührenordnung für Ärzte (Medical Fee Schedule)
hCG	human chorionic gonadotropin
HTA	health technology assessment
IGCCCG	International Germ Cell Cancer Collaborative Group
IGeL	Individuelle Gesundheitsleistung (individual out-of-pocket health service)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
PPV	positive predictive value
RCT	randomized controlled trial
SEER	Surveillance, Epidemiology, and End Results
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
TNM	tumour, node, metastasis
TSE	testicular self-exam
UICC	International Union Against Cancer
UK NSC	United Kingdom National Screening Committee
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

HTA overview

1 Background

1.1 Health policy background and commission

According to § 139b (5) SGB V (Social Code Book V, Statutory Health Insurance [SHI]), SHI members and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the ThemenCheck Medizin ("Topic Check Medicine") website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and to answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts together with a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about health care services and structures. This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

At a raw incidence rate below 11 per 100 000 men per year and accounting for only 1.6% of all cancers in men, testicular cancer is a rare cancer. The ranking of the most common cancers in men in Germany lists testicular cancer only in 14th place. Unlike in other cancers, however, most cases occur at an early age, between 25 and 45 years, making testicular cancer the most common malignant neoplasm in young men. In Germany, the median age at diagnosis is 38 years. The odds of developing testicular cancer over the course of a lifetime are 0.8%, and the lifetime risk of dying of testicular cancer is below 0.1%. The 5-year survival of testicular cancer patients registered in Germany is currently reported as 96% [1].

Testicular cancer is an umbrella term for malignant tumours developing from one or more cell types present in the male testicle. Testicular tumours are histopathologically classified using the revised World Health Organization (WHO) 2016 classification of testicular tumours [2–4]. About 95% of them are germ cell tumours, whereas tumours originating from other testicular cell types play only a minor role, being found in about 5% of cases [5]. The main types of germ

cell tumours are seminomas and nonseminomas, with the latter including multiple subtypes as well as mixed tumours with some seminoma component [5–7].

Nonseminomas are predominantly found in young men 20 to 30 years of age. Seminomas, in contrast, typically occur later in life (30–40 years of age) [4]. Some two-thirds of germ cell tumours registered in Germany are seminomas [1]. In 95% of cases, germ cell tumours originate in the testes; in the remaining 5%, the primary tumours are located outside the testes, typically along the midline of the body, and are referred to as extragonadal testicular tumours [5,6]. Synchronous bilateral testicular tumours are found in only 1–2% of cases [5].

Broadly speaking, germ cell tumours are categorized into three clinical stages:

- Stage I: localized tumour without lymph node or distant metastases
- Stage II: with retroperitoneal lymph node metastasis below the diaphragm
- Stage III: with lymph node metastasis above the diaphragm or distant metastasis.

Further clinical staging is based on the International Union Against Cancer (UICC) criteria for the TNM (tumour, node, metastasis) classification and the serum tumour markers of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) [8]. Table 1 and Table 2 present the UICC criteria for the classification of germ cell tumours (Table 1) and the resulting clinical staging (Table 2).

Table 1: TNM and tumour marker classification of germ cell tumours in accordance with UICC 2017

Primary tumour (T)	
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour (e.g. scar tissue)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or up to 5 lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or more than 5 lymph nodes, none more than 5 cm, or evidence of extranodal spread
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Localization other than M1a
Serum tumour markers (S)	
SX	Serum marker studies not available or not performed
S0	Serum marker study levels within normal limits
S1	LDH < 1.5 x N and hCG < 5000 (mIU/mL) and AFP < 1000 (ng/mL)
S2	LDH 1.5–10 x N or hCG 5000–50 000 (mIU/mL) or AFP 1000–10 000 (ng/mL)
S3	LDH < 10 x N or hCG < 50 000 (mIU/mL) or AFP < 10 000 (ng/mL)

Table 2: Staging of germ cell cancer in accordance with UICC 2017 (modified)

Tumour stage	Primary tumour (T)	Regional lymph nodes (N)	Distant metastases (M)	Serum tumour markers (S)
0	**Intratubular germ cell neoplasm (carcinoma in situ)**			
I	**Localized tumour without lymph node or distant metastasis**			
IA	pT1	N0	M0	S0
IB	pT2–T4	N0	M0	S0
IS	Any pT/TX	N0	M0	S1–3
II	**With retroperitoneal lymph node metastasis below the diaphragm**			
IIA	Any pT/TX	N1	M0	S0–1
IIB	Any pT/TX	N2	M0	S0–1
IIC	Any pT/TX	N3	M0	S0–1
III	**With lymph node metastasis above the diaphragm or distant metastasis**			
IIIA	Any pT/TX	N1–3	M1a	S0–1
IIIB	Any pT/TX	N1–3	M0	S2
	Any pT/TX	Any N	M1a	S2
IIIC	Any pT/TX	N1–3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

See Table 1 for the meaning of the indicated TNM and serum marker classifications.

Patients at metastatic stage are additionally classified as having a good, intermediate, or poor prognosis on the basis of their risk profile in accordance with the International Germ Cell Cancer Collaborative Group (IGCCCG) classification, which is based on the primary tumour site, the presence or absence of extrapulmonary organ metastasis, and/or serum tumour marker levels (AFP, hCG, LDH). In this system, seminomas are associated exclusively with a good or intermediate prognosis [5–7,9]. Accordingly, the 5-year survival for metastatic testicular cancer is between 86% (seminomas) and 92% (non-seminomas) in the good-prognosis group, between 72% (seminomas) and 80% (non-seminomas) in the intermediate-prognosis group, and 48% (exclusively non-seminomas) in the poor-prognosis group [9].

The causes of germ cell tumours are not completely understood. The risk has been found to be multiplied in men with a personal history (prior unilateral testicular cancer) or family

history (brother or father with testicular cancer), existing or past cryptorchidism (undescended testis), or infertility. Further suspected risk factors include toxic substances, prenatal oestrogen excess, Down syndrome, and various infectious diseases [10–12].

In Germany, testicular cancer is to be treated in accordance with clinical guidelines, e.g. the recommendations of the European Association of Urology [13], German Society for Haematology and Medical Oncology (DGHO) [5], or the European Society for Medical Oncology (ESMO) [6]. The primary therapy is removal of the affected testis (orchiectomy) via an inguinal incision. In case of an unclear diagnosis or small, isolated tumours, a frozen section biopsy can be initially performed at the exteriorized testis in order to rule out benign changes. Chemotherapy may be performed before orchiectomy in rare cases involving very advanced tumours and extensive metastasis. The postoperative procedure depends on tumour type, tumour stage, and risk profile in accordance with IGCCCG. The preferred approach for stage-I patients, particularly those without risk factors for occult metastasis, is active surveillance. The option of adjuvant chemotherapy to reduce the risk of recurrence exists only for patients with an unfavourable risk profile (nonseminomas with lymphovascular invasion, seminomas with tumour sizes > 4 cm). The guidelines recommend adjuvant radiotherapy only in exceptional cases. Irrespective of the chosen approach, cancer-specific survival of patients in stage I is about 99%. Seminoma patients in stage IIA/B undergo adjuvant radiotherapy (30–36 Gray) or multicycle chemotherapy. Stage IIA nonseminoma patients with normal tumour marker status are either placed on active surveillance with repeat imaging after 6 weeks or undergo retroperitoneal lymphadenectomy and further procedures based on histological results. Conversely, stage IIA/B nonseminoma patients with elevated tumour markers are treated like patients in more advanced IGCCCG stages. The long-term overall survival of stage IIA/B seminoma patients is reported as nearly 100%. In this stage, the cancer-specific survival of nonseminoma patients is about 98%. Seminomas in stage IIC or above as well as nonseminomas with elevated markers in stage II or above are treated with multicycle chemotherapy, where the number of cycles depends on the IGCCCG prognostic classification (3 cycles for good-prognosis group, 4 cycles for intermediate-prognosis and poor-prognosis group). The reported 5-year survival is about 90% for the good-prognosis group, 80% for the intermediate-prognosis group, and 50–70% for the poor-prognosis group [9,14]. It is important to note that, in nonseminoma patients, any postchemotherapy residual metastases > 1 cm must be removed due to the risk of teratoma. In seminoma patients, in contrast, postchemotherapy lymphadenectomy is indicated only if the size of the retroperitoneal lymph nodes remains > 3 cm and fluorodeoxyglucose positron emission tomography shows positive findings.

Comprehensive investigations have demonstrated the effectiveness of chemotherapy for testicular cancer. However, few studies are available on potential treatment-related harms [7,15]. In addition to the acute adverse impacts of therapy, late toxicities of radiochemistry

and chemotherapy might be of particular concern. Alongside the development of secondary tumours, this includes toxic effects on the lung, nervous system, hearing, and endocrine functions as well as chronic fatigue. Further, fertility might be impaired as a consequence of radiotherapy and/or chemotherapy [5,7].

Currently, 75% to 80% of seminomas and some 55% of nonseminomas are discovered in the prognostically most favourable stage I, which is associated with about 99% cancer-specific survival [13,16]. In most cases (> 85%), the main reason for the initial office visit is a painless swelling or palpable hardening of the testis, as noticed by the patient himself [7].

The poorer prognosis and more aggressive therapy associated with some advanced tumour stages raise the question of whether screening programmes might be of benefit. Conceivable screening measures might include, for instance, encouraging and instructing young men to perform systematic testicular self-exams (TSE) or regular clinical palpation and scrotal ultrasound for young men in the context of a screening programme. On the basis of a systematic review (updated in 2014) of the available evidence on the potential benefits and harms from testicular cancer screening, the United States Preventive Services Task Force (USPSTF) advises against introducing screening. USPSTF's main arguments for advising against screening (grade D recommendation) are the rarity of the disease and the lack of evidence of a net benefit of screening [15,17]. A Cochrane review published in 2011 likewise reports that no randomized screening studies are available [18]. Proponents of testicular cancer screening criticize this rejection for lack of studies, because it might discourage men from performing TSE, which they deem sensible, and they call for the USPSTF recommendation to be qualified [19,20]. The high cost of treatment in more advanced tumour stages is another argument of TSE proponents. According to a cost-benefit analysis, the potential prevention of 1 advanced tumour through TSE would result in savings equal to the cost of more than 300 diagnostic evaluations of suspected cases, which might occur in greater numbers [21]. In Germany, men 45 years of age and older are eligible for 1 annual inspection and palpation of the external genitals as part of the statutory cancer screening programme [1].

2 Research questions

The aims of this investigation are to

- assess the benefit of testicular cancer screening through clinical palpation and scrotal ultrasound or through testicular self-examination (TSE) in men from 16 years of age in comparison with no screening with regard to patient-relevant outcomes,
- determine the cost (intervention cost) arising from testicular cancer screening in comparison with no screening in asymptomatic men from 16 years of age,
- assess the cost-effectiveness of testicular cancer screening in comparison with no screening in asymptomatic men from 16 years of age, and
- review ethical, social, legal, and organizational aspects associated with the screening.

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment was asymptomatic men from 16 years of age. The experimental intervention was testicular cancer screening by regular TSE (self-palpation) or clinical palpation in combination with scrotal ultrasound. There were no restrictions regarding the frequency of examinations. The comparator intervention was no testicular cancer screening (i.e. the current situation with men aged 45 years and older being eligible for an annual inspection and palpation of the genitals as part of cancer screening).

The investigation examined the following patient-relevant outcomes:

- Mortality, such as
  - overall survival
  - disease-specific mortality (testicular cancer mortality)
- Morbidity, such as
  - incidence of prognostically unfavourable, advanced cancer stages (stage shift)
- Adverse events (AEs), such as
  - false-positive and false-negative screening results
  - adverse treatment effects (including late toxicities)
  - overdiagnosis and overtreatment
- Health-related quality of life

Subjective outcomes (e.g. health-related quality of life) were to be included only if they were surveyed using valid measuring instruments (e.g. validated scales).

Randomized controlled trials (RCTs) and non-randomized, prospectively planned, comparative interventional studies with concurrent control group and adequate confounder control were to be included in the benefit assessment. There were no restrictions regarding the study duration.

A systematic search for primary literature was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database. In order to do justice to the advancements in chemotherapy, the included studies had to be published no earlier than 1990.

The following sources of information and search techniques were additionally used: study registries, systematic reviews as well as documents made available from commenting procedures.

Relevant studies were selected by 2 reviewers independently from one another. Any discrepancies between the reviewers were resolved by discussion between them.

If suitable studies were identified, the following further steps would need to be taken: data extraction into standardized tables, assessment of the risk of bias at study and outcome levels, each as low or high to assess the qualitative certainty of results, description of results of the individual studies broken down by outcomes, preparation of a qualitative summary in the form of metaanalyses in case of similar research questions and sufficient homogeneity of studies as well as generation of an evidence map of (greater) benefit and (greater) harm in 4 levels based on certainty of results. The four possible levels are proof (highest certainty of results), indication (moderate certainty of results), hint (weakest certainty of results), and either no data available or the available data do not permit drawing any of the other 3 conclusions. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

3.2 Methods – supplementary presentation for the benefit assessment

Particularly in cases where no interventional studies are available across the entire screening chain up to results on patient-relevant outcomes, the evidence on relevant subordinate screening aspects, the diagnostic quality of screening and diagnostic evaluation, and the benefits of earlier therapy were to be assessed to supplement the benefit assessment. For this purpose, focused, systematic searches were conducted for diagnostic studies, systematic reviews on therapeutic studies, and modelling studies.

Diagnostic studies

The target population of diagnostic studies was asymptomatic men from 16 years of age. The index test was testicular cancer screening via (1) TSE (self-palpation) and, in case of suspicious findings, followed by combined clinical palpation and scrotal ultrasound, or (2) combined clinical palpation and scrotal ultrasound alone. The reference test was a histological evaluation of frozen sections or the resected testis. For the investigation, the following outcomes were examined:

- sensitivity, specificity, predictive values
- stage-specific detection rates

To be included were diagnostic studies on men who were screened and promptly (re)examined with the reference test. No conclusion on benefit was to be derived from the supplementary presentation of diagnostic studies.

A systematic search in the form of focused information retrieval was conducted in the databases MEDLINE and Cochrane Central Register of Controlled Trials. Studies published in or after 1980 were included.

The following sources of information and search techniques were additionally used: study registries and documents made available from commenting procedures.

The references were selected by 1 reviewer, and quality assurance was performed by a 2nd reviewer.

If suitable studies were identified, the following steps would need to be taken: data extraction into standardized tables, outcome-specific assessment of the risk of bias, and a comparative description of the results of the individual studies, broken down by outcomes.

Studies comparing early treatment (diagnosed by screening) versus late treatment (diagnosed due to symptoms)

Therapeutic studies which allow a comparison of treatment effects in patients with early treatment start (i.e. corresponding to the screening situation) versus late treatment start (i.e. corresponding to the non-screening situation) were to be used to assess any potential benefits of an earlier treatment start. The target population consisted of previously untreated testicular cancer patients from 16 years of age. Some of the patients had to have been identified through screening or exhibit characteristics (particularly stage distribution) which indicate with sufficient certainty an early treatment start (transferable to the screening situation).

The intervention to be tested was treatment comparable to a screening situation, i.e. of more early cancer stages, in accordance with the current guideline or the guideline-compliant treatment of a screened population. The comparator intervention was treatment comparable to a no-screening situation of later-detected cancer stages in accordance with the current guideline or the guideline-compliant treatment of an unscreened population. The following patient-relevant outcomes were to be examined:

- Mortality, such as
  - overall survival
  - disease-specific mortality (testicular cancer mortality)
- Morbidity, such as
  - recurrence rates
- AEs, such as
  - adverse treatment effects (incl. late toxicities)

- Health-related quality of life

Subjective outcomes (e.g. health-related quality of life) were to be included only if they were surveyed using valid measuring instruments (e.g. validated scales). Randomized therapeutic studies to be included were those which allowed drawing comparative conclusions with regard to the effectiveness and/or safety of treatment in early and late stages of testicular cancer. This includes studies with a comparison of treatment effectiveness and/or safety, stratified either by tumour stages (early or advanced stages) or by detection mode (clinically or through screening). The studies had to have a follow-up of at least 5 years.

A systematic literature search for relevant systematic reviews of such studies was conducted in the MEDLINE, Cochrane Database of Systematic Reviews, and HTA databases. In order to do justice to the advancements in chemotherapy, the included studies had to be published no earlier than 1990.

The references were selected by 1 reviewer, and quality assurance was performed by a 2nd reviewer.

Registry studies: Survival time by tumour stage

Given that the perusal of the systematic reviews, which was done as part of the literature selection process, revealed that such subgroup comparisons are unlikely to exist, the identification of further primary studies was discontinued. Publications on the stage-specific prognosis of survival time in testicular cancer, which had already been found in the selection for the benefit assessment, were used instead.

The target population for registry studies was testicular cancer patients from 16 years of age.

For the investigation, the following outcomes were examined:

- Stage distribution of testicular cancer
- Stage-specific mortality

The data had to be transferable to Germany and provide information of acceptable quality on the stage distribution of testicular cancer.

The references identified for the benefit assessment were used for the selection.

The references were selected by 1 reviewer, and quality assurance was performed by a 2nd reviewer.

All information necessary for the assessment was extracted in tabular form from the documents on the included publications and described in the text.

No benefit assessment was derived from the supplementary presentation on the benefit of earlier treatment.

Decision analysis modelling studies

Model-based benefit-harm decision analyses represent an assessment approach based on systematic evidence linkage which allows integrating all evidence subareas relevant for the assessment of screening measures [22–24]. Therefore, another supplementary presentation involved a search for model-based benefit-harm analyses of testicular cancer screening.

The target population of the benefit assessment was asymptomatic men aged 16 years and older. The experimental intervention was testicular cancer screening by regular TSE (self-palpation) or clinical palpation in combination with scrotal ultrasound. There were no restrictions regarding the frequency of examinations. The comparator intervention was “no screening for testicular cancer”.

For the investigation, the following patient-relevant outcomes were to be examined:

- Mortality, such as
  - overall survival
  - disease-specific mortality (testicular cancer mortality)
  - life years gained
- Morbidity, such as
  - quality-adjusted life years gained
  - Avoided advanced cases (stage shift)
- AEs, such as
  - false-positive and false-negative screening results
  - Adverse treatment effects (including late toxicities)
  - Overdiagnosis and overtreatment

Items to be included were pure benefit-harm analyses as well as benefit models generated as part of a complete model-based economic evaluation (cost-effectiveness/utility/benefit analysis).

A systematic search as part of focused information retrieval was conducted in MEDLINE, Embase, and HTA database. Studies published in or after 1990 were to be included.

The following sources of information and search techniques were additionally used: systematic reviews as well as documents made available from commenting procedures.

The hits found in the focused search were selected by 1 person, and quality assurance was performed by a 2nd person.

If suitable studies had been identified, the following steps would have been conducted: data extraction into standardized tables, assessment of report quality, assessment of the transferability of results, and comparative description of the individual studies' results. No conclusion on benefit was derived from the supplementary presentation of modelling studies.

3.3 Methods – health economic assessment

To calculate the intervention costs, the average resources directly required when performing the experimental and comparator intervention were determined. For this purpose, in addition to the experimental and comparator interventions, the services directly associated with the intervention were taken into account. The relevant regulated or negotiated prices of these services were used wherever possible. Reimbursable and non-reimbursable costs were listed separately.

For the systematic review, cost-effectiveness/efficacy analyses, cost-utility analyses, or cost-benefit analyses (in the narrower sense) published in or after 1990 were to be included. No geographic limitations were put in place.

For assessing health economic aspects, a systematic search in the form of focused information retrieval was carried out in the MEDLINE and Embase databases. In parallel, a search for relevant systematic reviews was conducted in MEDLINE, Embase, and HTA Database. Studies published in or after 1990 were included.

The following sources of information and search techniques were additionally used: systematic reviews as well as documents made available from commenting procedures.

The references were selected by 1 reviewer, and quality assurance was performed by a 2nd reviewer.

If suitable studies were identified, the following steps would need to be taken: data extraction into standardized tables, assessment of report quality, assessment of the transferability of results, and comparative description of the individual studies' results.

3.4 Methods – ethical aspects

Ethical aspects were identified and evaluated using 4 complementary approaches: (1) analytically on the basis of established normative frameworks, (2) through scoping searches in the scientific literature, (3) through searches in non-scientific information sources in the Internet, and (4) through a target group survey regarding ethical implications.

On the basis of a normative framework for the ethical evaluation of public health measures [25], the ethical issues raised by testicular cancer screening were investigated with regard to the various ethical evaluation criteria. This process included determining the extent to which Hofmann's questionnaire [26] might result in further ethically relevant aspects to be taken into account in the present HTA.

- To identify ethical aspects of testicular cancer screening as well as of cancer screening in general, a scoping search was conducted in the Pubmed, EthicsWeb, Google Scholar, and ETHMED databases. In addition, a search for non-scientific information was conducted on the websites of relevant institutions and interest groups.

One reviewer screened the information from all information sources found in the scoping searches to identify statements on ethical arguments and aspects of testicular cancer screening. The result underwent quality assurance by a 2nd person.

A structured survey of 5 young men without the disease and 1 former testicular cancer patient was conducted using an interview guide whose questions were based on the ethical aspects identified analytically and in the searches. The discussions with the interviewees were recorded and analysed for content.

The ethical assessment of potential benefits and harms as well as of the cost effectiveness of testicular cancer screening utilized the results of the HTA report's domains "benefit assessment" and "economic assessment". In addition, relevant social, legal, and organizational aspects were integrated.

All relevant arguments and aspects from the various sources of information were extracted into tables and organized in accordance with the normative framework [25]. In addition, ethical implications were identified as representing (1) issues concerning the implementation of individual ethical requirements or (2) conflicts between ethical requirements.

The individual ethical implications were weighted with regard to their relevance to the use of testicular cancer screening. Afterwards, the results were presented to the other reporters and jointly examined for their plausibility. Together, the reporters determined (1) how the ethical requirements can be optimally implemented in testicular cancer screening and (2) how any potentially resulting conflicts between individual requirements can be handled in an ethically justifiable manner.

3.5 Methods – social, legal, and organizational aspects

Social aspects

In the HTA, social and sociocultural aspects address the mutual interactions between examination/treatment methods and the social environment (e.g. resource distribution in a society, access to technologies, patient preferences, social norms, and values).

The information processing on social aspects was based on the comprehensive conceptional framework suggested by Mozygemba 2016 [27] and the questions (assessment elements) of the HTA Core Model from EUnetHTA [28].

Proceeding from this, content categories were formed for the analysis of the identified studies:

- Knowledge about testicular cancer
- Knowledge about and prevalence of TSE
- Reasons for and factors influencing the (non)practice or intention to practise TSE (psychosocial aspects, information and/or knowledge status, risk awareness as well as personal attitudes, sociodemographic factors, and health behaviours)
- Education about testicular cancer and TSE received by healthcare staff
- Information sources as well as desired information on testicular cancer and TSE

The results were processed in tabular and descriptive form in accordance with the content categories.

Scoping searches were conducted for the analysis of social aspects. The scoping searches were carried out in the following information sources:

- MEDLINE
- Social Science Citation Index (SSCI)
- Data from national and regional registries
- Information from laws, regulations, or guidelines
- Interest group-based information sources, e.g. stakeholder websites
- Studies included for the benefit assessment and economic assessment regarding social, legal, and organizational aspects/arguments

One reviewer screened the information from all information sources found in the scoping searches to identify statements on social, legal and/or organizational arguments and aspects of the technology to be investigated. The result was scrutinized for quality by a 2nd person.

The survey of affected men described in Section 3.4 was also subjected to content analysis in search of information on social aspects concerning testicular cancer and TSE.

Legal aspects

SGB V, the G-BA Rules of Procedure on screening measures, and its cancer screening guidelines were used as sources on legal aspects and were analysed in accordance with the contents provided therein.

Organizational aspects

As sources on organizational aspects of suitable screening measures, the criteria of Wilson and Jungner [29], the UK National Screening Committee [30], and the book “Screening. Evidence and Practice” by Raffle and Gray [31] were used, viewed, and relevant text passages excerpted.

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

The information retrieval found neither randomized controlled studies nor nonrandomized prospective, comparative interventional studies with concurrent control group to answer the research question of the benefit assessment.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 7 November 2018. No ongoing studies were identified. The most recent search was conducted on 15 January 2019.

4.2 Results of the benefit assessment

Since no suitable studies were found, no conclusions can be drawn on the benefits and harms of testicular cancer screening. There is no hint of (greater) benefit or (greater) harm.

5 Results: Supplementary presentations to the benefit assessment

5.1 Supplementary presentation of results from diagnostic studies

The aim of the supplementary presentation was to identify diagnostic studies which revealed information on the diagnostic quality of testicular cancer screening by TSE or clinical palpation in combination with scrotal ultrasound with regard to the detection of testicular cancer in an asymptomatic screening population or the frequency of harms due to false-positive and false-negative screening results.

The focused information retrieval for the supplementary presentation of diagnostic studies found no study which met all inclusion criteria and provided usable data on the quality of the investigated screening methods in an asymptomatic screening population.

However, the search found several studies which contain information on relevant aspects of the investigated methods and are usable for roughly estimating the potential harm associated with their use. These excluded studies were marked and extracted as additional literature of interest. In addition to 8 studies providing additional information of interest from the focused search for diagnostic studies [14,32–38], 4 other diagnostics-related studies were found in the systematic search for the benefit assessment and included [39–42]. These studies provided data on the positive predictive value (PPV) – i.e. the probability of the disease being present in men with abnormal test results – as well as on unnecessary testicular exploration or removal resulting from diagnostic evaluation after a medical examination. The medical examination consisted of either a combined clinical exam and scrotal ultrasound, or a palpation exam alone, or scrotal ultrasound due to a clinically suspected tumour. Two studies [32,39] were used to collect evidence on the magnitude of the potentially adverse impacts of TSE.

5.1.1 Adverse impacts of clinical testicular examination (testicular anomalies requiring diagnostic evaluation and unnecessary testicular exploration)

Potential harms from screening are predominantly the result of the limited capability of sonography to differentiate between malignant and benign lesions [43,44]. Hence, definitive diagnostics often require histopathological examination of the surgically exposed or removed testis. Since, in case of non-malignant findings, testicular exploration or removal can be deemed unnecessary harm, this investigation aimed to collect data on the frequency of unnecessary invasive procedures resulting from the use of screening. Noncancerous anomalies detected during a targeted testicular examination, such as varicoceles, hydroceles, and cysts, represent another problem: While they typically do not require treatment, they might worry patients and lead to the increased use of medical resources for further diagnostic evaluation. Any adverse impacts of clinical testicular exams were determined on the basis of

studies providing data for calculating PPVs of screening exams or data on the prevalence of testicular anomalies found in the examinations.

Table 3: PPV and proportion of unnecessary testicular explorations or removals following clinical palpation and scrotal ultrasound

Study	Study population	Number of participants	Study objective	Examin-ation type	Number of TC / number with abnormal results	PPV	Unnecessary procedures / testicular exposure or removal in total
Asymptomatic population							
Peterson 2001 [41]	Voluntary sampling of asymptomatic U.S. Army service members 18–35 years of age	1504	Association between microlithiasis and testicular cancer	CPE and US	1/3	33%	2/3 (67%)
Roemer 2006 [42]	Asymptomatic 19-year-old draftees at muster in Germany 2001–2003	1600	Not stated	CPE	0/0	-	NR[a]
Casey 2009 [39]	Bank employees voluntarily participating in a screening	677	Frequency of TSE; prevalence of benign anomalies	CPE	0/8	-	0/0 [b]
Preselected study population							
Geczi 2001 [32]	Men with complaints who presented to a urology clinic as part of a prevention campaign after performing TSE	2342	Can TSE lead to the earlier detection of TC?	CPE and US	26/31	84%	5/31 (16%)
Isidori 2014 [33]	Solid intratesticular lesions identified by US	197, of which 115 non-palpable	US quality in nonpalpable small lesions	US	126/197	64%	46/172[c] (26%)
Kennedy 1999 [34]	Retrospective analysis of patients with intratesticular lesions from 661 consecutive US	44 (41)[d]	Clinical consequences and quality of US	US	19/41	46%	12/31 (39%)

Study	Study population	Number of participants	Study objective	Examination type	Number of TC / number with abnormal results	PPV	Unnecessary procedures / testicular exposure or removal in total
Kuhn 1984 [35]	Clinically suspected TC	54	Value of US in the differential diagnostics of palpable changes	US	8/10	80%	2/10 (20%)
Moore 2009 [40]	Diagnostic evaluation of swelling suspected to be cancerous, referred by GP	143	Experience with "one-stop clinic" as contact point in case of worrisome symptoms	US	14/14	100% [e]	0/14 (0%)[e]
Polak 1990 [36]	Clinically suspected testicular cancer	56	US test quality for TC	US	35/43	81%	8/43 (19%)
Rizvi 2011 [37]	Scrotal swelling	120, of which 22 with testicular mass	US test quality	Colour Doppler US	14/16	88%	2/16 (12%)
Robertson 1995 [38]	Retrospective analysis of testicular exploration and removal due to suspected TC	149	Identification of factors which help avoid unnecessary testicular exploration and removal	US in 44%	102/132 102/149	77%[f] 68%[g]	30/132 (23%)[f] 47/149 (32%)[g]
Van Dijk 1994 [45]	Suspected TC based on palpation	411	US test quality	US	18/23	78%	5/23 (22%)

NR: not reported; TC: testicular cancer; CPE: clinical palpation exam by physician; PPV: positive predictive value; TSE: testicular self-exam; US: ultrasound

[a] 0.19% of draftees examined between 1983 and 1998 underwent diagnostic evaluation due to suspected TC.
[b] All abnormalities were diagnostically evaluated using US; no invasive procedures were performed for diagnostic evaluation.
[c] The remaining 25 were diagnostically evaluated via clinical follow-up.
[d] Only 41 of them were suitable for analysis.
[e] It is unclear whether there were indeed no false positive cases.
[f] Orchiectomy.
[g] Orchiectomy or testicular biopsies.

The data extracted from the 12 studies on clinical testicular exams involving a total of 7297 patients, (see Table 3) show that about 12–67% of the testicular explorations carried out as part of diagnostic evaluation of testicular cancer resulted in benign findings and hence might have been unnecessary. Three studies (3781 patients) had investigated an asymptomatic population. However, no testicular cancer occurred in 2 of these studies. Therefore, it was possible to calculate a PPV for asymptomatic participants solely on the basis of the Peterson study. It had the lowest PPV of 33%, i.e. 33% of men with abnormal findings actually had testicular cancer [41]. Even in a selected population of men with scrotal swelling, 12% of ultrasound findings suspicious for malignancy were false positive, and 33% of the findings deemed benign were false negative [37]. Further, it was found that a substantial number of noncancerous anomalies are discovered by clinical palpation and particularly by scrotal ultrasound; this causes worries in the affected men and might contribute to a greater consumption of medical resources due to further diagnostic evaluation. Isidori [33] illustrated that a very high percentage of nonpalpable lesions detectable only by ultrasound are benign and showed that, due to the various reasons for referral, the results of diagnostic studies with patients referred for ultrasound are difficult to transfer to a screening population. The considered studies fail to show whether and to what extent clinical screening contributes to the prevention of advanced stages of testicular cancer and mortality. Likewise, the studies do not allow comparing clinical screening versus no clinical screening in terms of unnecessary testicular exploration. False-negative findings were rare and found primarily in studies histologically examining even ultrasound findings which were not suspicious for malignancy [36,37].

5.1.2 Adverse impacts of TSE (testicular anomalies requiring diagnostic evaluation and unnecessary testicular exploration)

The search did not find any studies on the prevalence of TSE in Germany or on the number of clinical evaluations performed based on concerns from TSE.

The study which comes closest to answering the research question is a Hungarian study by Geczi et al. [32], which was listed as additional literature of interest. The study describes the findings from 5056 men who voluntarily underwent a testicular exam and ultrasound at a hospital specializing in testicular cancer. Their participation followed a 1995 media awareness campaign about the importance of testicular cancer screening and performing TSE. In case of findings which were suspicious for cancer, tumour markers were additionally measured and invasive diagnostics performed, if appropriate. A total of 2342 of the 5056 volunteers presented due to various complaints. We assume this to be precisely the group which would see a physician after TSE. Outside a study setting, the other, no-complaints group would presumably not see a physician and hence, no harm from diagnostic evaluation could arise. Therefore, we used the group with complaints as the basis for calculating potential harms. In 1810 men (77%) of this group, the medical examination revealed a testicular anomaly. Further

urological evaluation was necessary in 3.9% of the complaints group. In 31 (1.3%) of the men presenting with complaints, clinical examination and ultrasound resulted in suspected testicular cancer, which was confirmed by subsequent invasive diagnostic evaluation in 26 cases. Nineteen (73%) of the 26 malignant tumours were in stage I. In the remaining 5 suspected cases (16%), the invasive examination did not reveal any malignancies. Assuming that the study's group with complaints represents men who – even outside a study setting – would visit a physician if they found abnormalities in the TSE, a PPV of 1.1% (26/2342) can be derived for TSE (Table 4). The PPV of clinical examination and scrotal ultrasound in a population preselected through TSE would be 84% (26/31) (also see Table 3). The study provides only part of the information necessary to estimate negative impacts in a TSE setting since it does not reveal which percentage of the population reached by the media awareness campaign is represented by the complaints group included in the study. Since no comparison is available with men who were not exposed to the awareness campaign, it is impossible to determine whether the media-based encouragement to perform TSE contributed to the reduction of advanced stages of testicular cancer and mortality. Given the unproven and likely small benefit and the large number of incidental findings, the authors recommend limiting TSE to high-risk groups.

Table 4: PPV and proportion of unnecessary testicular exploration or removal following TSE

Study	Study population	Number of patients	Study objective	Examination type	Number of TC / number with abnormal results	PPV	Unnecessary procedures / testicular exposure or removal in total
Geczi 2001 [32]	Men with complaints who, as part of a prevention campaign, presented to a urology clinic after TSE	2342	Can TSE lead to the earlier detection of TC?	TSE	26/2342	1%	5/2342 (0.2%)
PPV: positive predictive value; TC: testicular cancer; TSE: testicular self-exam; US: ultrasound							

5.2 Supplementary presentation of results on the benefit of earlier treatment

Studies based on cancer registries were used because the screening of 16 systematic reviews of therapeutic studies on testicular cancer showed there are presumably no therapeutic studies allowing a comparison of treatment effects in patients with early treatment start (corresponding to a screening situation) versus late treatment start (corresponding to a no-screening situation).

The supplementary presentation of results from cancer registries is intended to explore the potential added benefit resulting from starting treatment in earlier disease stages. For this purpose, the distribution of testicular cancer stages and stage-specific mortality were determined from registry data.

Two studies with appropriate data from cancer registries were found [46,47].

Minicozzi (2017) [47] analysed the quality of stage information for 15 cancer types diagnosed in 2000–2007 as reported to EUROCARE by 62 European cancer registries and provided age-standardized relative 5-year survival rates for local, regional, and metastatic tumour stages. The overall assignment to the three stages of tumour spread was carried out either by the reporting tumour registries themselves or else determined on the basis of detailed or condensed TNM data. Results were reported by the type of reported data. Table 5 shows the average distribution of testicular cancer stages at the time of diagnosis on the basis of data from 12 881 testicular cancer cases from 8 selected cancer registries with qualitatively acceptable TNM information as well as the distribution of summarized stages reported from Austria, which was included in the table to replace missing data from Germany. On the basis of the data, the percentage of testicular cancer cases detected in the prognostically unfavourable metastatic stage can be estimated as 6–11%. Age-standardized relative 5-year survival for the local, regional, and metastatic testicular cancer stage was presented in the appendix of the publication in the form of box plots stratified by the type of reporting data.

Table 6 shows the approximate medians read off of the figures for the distribution of stage-specific relative survival based on data reported to various tumour registries. The box plots did not show which registries were included in each analysis. When compared to the high relative survival rates of 99% in the local stage and 86% in the regional stage, survival rates in the metastatic stage were far lower, at values between 67% and 81%.

Table 5: Distribution of testicular cancer stages at diagnosis based on the reporting data from various European tumour registries in 2000–2007 by type of underlying stage information (in percent)[47]

	Type of stage information		
	TNM (Cancer registry with acceptable data quality)	**Condensed TNM (Cancer registry with acceptable data quality)**	**Tumour spread Local/regional/metastatic (Austria)**
Local	50	56	73
Regional	14	19	13
Metastatic	11	11	6
Incomplete	21	2	0
No data	3	13	8
TNM: tumour, node, metastasis classification			

Table 6: Medians of the distribution of age-standardized relative 5-year survival rates based on reporting data from various European cancer registries in the period 2000–2007 by testicular cancer stage and type of underlying stage information in percent[47]

	Type of stage information		
	TNM	**Condensed TNM**	**Tumour spread local/regional/metastatic**
Local	99	99	99
Regional	96	96	96
Metastatic	77	81	67
Incomplete	97	98	>90
No data	95	95	96
TNM: tumour, node, metastasis classification			

Available U.S. data paint a similar picture. Gandalia (2014) [46] analysed data of 31 330 patients from the Surveillance Epidemiology and End Results (SEER) database who were diagnosed with testicular cancer between 1993 and 2009. Cancer-specific 15-year mortality rates for seminoma patients were 0.4% when diagnosed in the local stage, 2.4% when diagnosed in the regional stage, and 10.8% when diagnosed in the metastatic stage. Cancer-specific 15-year mortality rates for non-seminoma patients were 1.6% for patients diagnosed in the local stage, 3.1% in the regional stage, and 19.6% in the metastatic stage. SEER data from 2009–2015 are available online [48] and show that testicular cancer was detected in the local stage in 68% of cases, in the regional stage in 19% of cases, and in the metastatic stage in 12% of cases. The relative 5-year mortality rate for testicular cancer in the local stage is 99%, in the regional stage, 96%, and in metastatic stage, 73%.

Since European and U.S. registry data show the survival rates of patients in the local stage and regional stage to be reduced very little, any medical benefit of testicular cancer screening would have to largely result from the prevention of metastatic stages. However, alongside differences in survival rates, the assessment of potential benefit must take into account the low prevalence of metastatic stages, of approximately 6–11%, even in the absence of screening. Furthermore, it must be noted that even metastatic testicular cancer is classified by IGCCCG into tumours with good, intermediate, and poor prognoses [9], thereby further reducing the target group of men whose lives might be saved by earlier diagnosis. It is important to be aware that the stage distributions and survival rates derived from the registry data reflect the current situation without established screening. The registry data do not show whether and to what extent screening programmes might contribute to the prevention of advanced stages of testicular cancer and the reduction of mortality. However, the information obtained as part of this supplementary presentation does allow roughly estimating the maximum theoretically possible benefit of screening based on the assumption that all cases currently detected in the metastatic stage are preventable by way of screening and that the survival rate correspondingly increases as a result of earlier treatment.

5.3 Supplementary presentation of results from modelling studies

The information retrieval found no modelling studies on testicular cancer screening. The most recent search was conducted on 7 November 2018.

5.4 Discussion

The systematic search for comparative interventional studies covering the entire screening chain was unsuccessful. Therefore, no robust evidence is available to draw any conclusions on any added benefit of screening via TSE or via clinical palpation and scrotal ultrasound when compared to no screening in asymptomatic men from 16 years of age. There is no hint of (greater) benefit or (greater) harm. The present report did not explicitly investigate screening programmes focusing exclusively on men at higher risk of testicular cancer. This was because the majority of men with known risk factors (prior unilateral testicular cancer, father or brother with testicular cancer, infertility examinations) are believed to already be specifically examined for testicular cancer. Our extensive search shows, however, that no interventional studies on the benefit of screening high-risk populations are available either, and hence, no conclusions can be drawn even for this population. However, in general, the benefit–harm relationship of screening measures increases with the risk of disease.

The absence of corresponding benefit studies is confirmed by the systematic reviews included as part of the search [18,49,50]. In addition, the more current, unchanged evidence situation in 2014 and March 2019 is reported on the websites of USPSTF and the PDQ Screening and Prevention Editorial Board of the U.S. National Cancer Institute [51]. All reviews conclude that

the potential added benefit of screening is low due to the low incidence and high cure rates of the disease.

No references meeting the inclusion criteria were found in the searches conducted as part of the supplementary presentation to the benefit assessment; these searches looked for studies on the accuracy of the investigated screening procedures in an asymptomatic screening population or on the benefit of earlier treatment or for modelling studies. The supplementary searches did, however, find several studies containing some information relevant for assessing the screening; these studies were recorded and analysed as additional literature of interest in the individual parts of the supplementary presentations.

The supplementary presentations on the benefit assessment reveal that some important information which would be required for a model-based evaluation of the benefit of testicular cancer screening is missing. For instance, no evidence is available on whether and to what extent screening actually contributes to the prevention of advanced testicular cancer stages and the associated mortality and how it impacts the number of unnecessary testicular exposures. With the aid of assumptions, the information obtained as part of the supplementary presentations can be used to assess the theoretically possible benefit and harm. However, due to missing data on individual subareas, this is possible only to a limited extent. The data and data gaps found in the weighing of benefit and harm can be presented in the form of flow diagrams, which use the available data to compare the number of expected benefit and harm events in case of TSE, clinical examination, and no screening.

The flow diagram in Figure 1 presents the available data for estimating the effects of screening on the expected distribution of tumour stages at diagnosis and cancer-related mortality and hence focuses on the benefit aspects of screening. The flow diagram illustrates the lack of data on screening exams which would be necessary for the benefit assessment. However, relying on the incidence and mortality rates in Germany in addition to assumptions, the researchers were able to use the data on the no-screening situation to estimate the maximum possible benefit of screening. The figure shows that in the current no-screening situation, 11 cases of testicular cancer per 100 000 men are detected annually [1]. On the basis of the stage distribution extracted from Minicozzi [47] (Table 5), this population would include 0.7–1.2 patients with metastatic tumours and substantially reduced survival rates when compared to the normal population. Every year, there are 0.4 deaths from testicular cancer per 100 000 men [1]. Under the extreme assumption that all tumours detected in the local and regional stages are curable and all cases detected in the metastatic stage could be prevented by screening, for every 100 000 men participating in screening every year, no more than 1.2 advanced tumours and 0.4 deaths could be prevented. This would mean that the estimated maximum benefit of testicular cancer screening is one hundred times lower than

the benefit of the established colon cancer screening with colonoscopy, which has been reported as 30–60 prevented deaths per 100 000 annually in 55-year-old men [52].

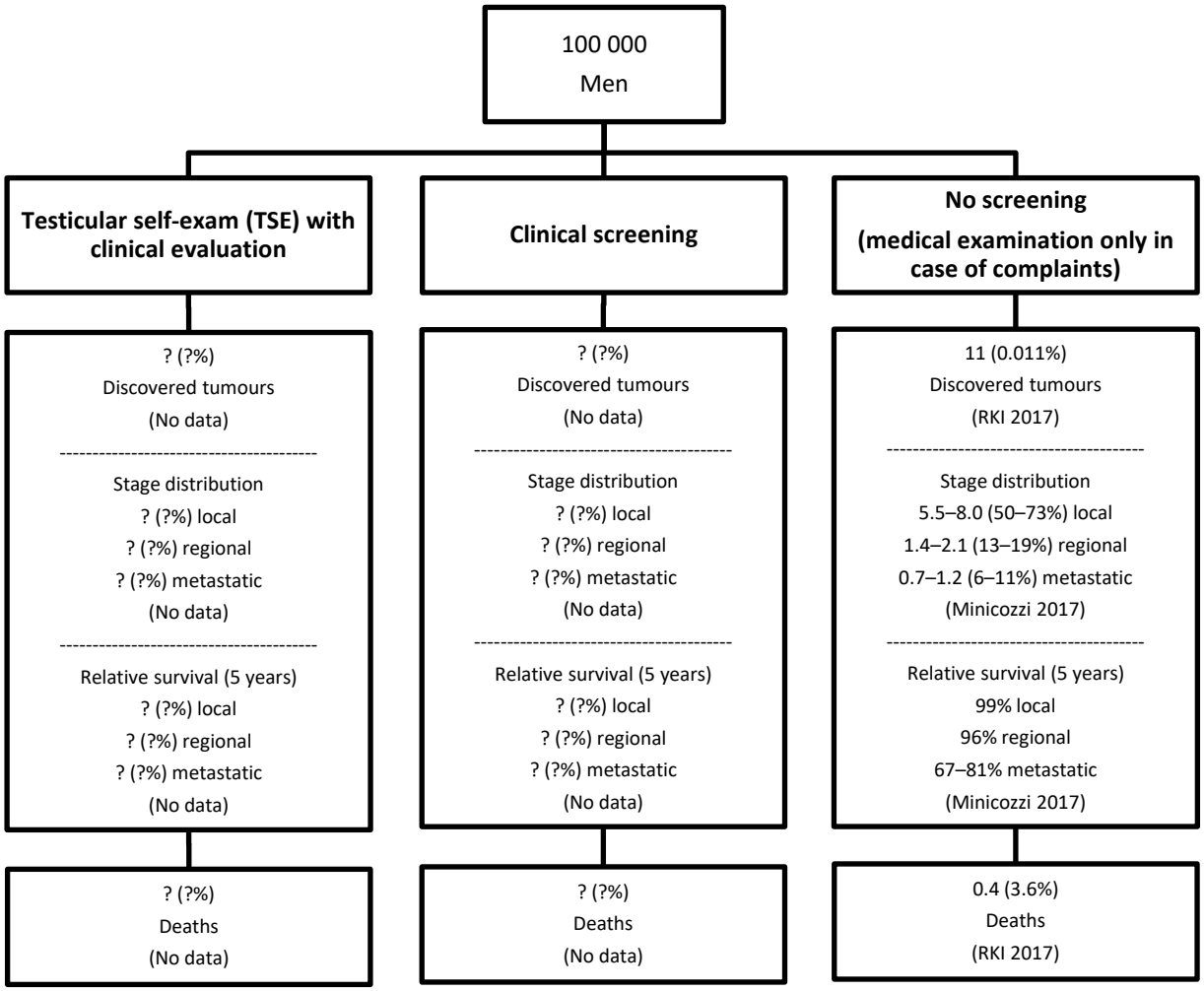

Figure 1: Flow diagram for estimating the benefit of testicular cancer screening

The flow diagram in Figure 2 focuses on the harm aspects of screening. It shows the available data for estimating the effects of screening on the number of discovered testicular abnormalities, more extensive urological evaluations, and testicular exploration/removal with malignant and benign definitive findings. The flow diagram illustrates that there is a lack of the data required to evaluate the harm caused by the current no-screening situation. Due to the missing data, the added harm to be expected in case of screening cannot be quantified. The data found as part of the supplementary presentation can be used only for estimating harm events in case of screening. However, this again requires making assumptions and using incidence rates from Germany. The figure shows that, in case of TSE screening, 991 of 100 000 men notice a worrisome change during one of their TSEs, resulting in an office visit. No empirical data on the prevalence of worrisome findings in TSEs were available. Therefore, the number of worrisome findings per 100 000 men was calculated backwards on the basis of the

prevalence of confirmed cases of testicular cancer (n = 26) found in the Gezci study [32] within the population of men with office visits due to complaints after being instructed on how to perform TSE (n = 2342) and the testicular cancer incidence in Germany (11/100 000) as follows (2342/26)*11=991. It is important to note that the use of German incidence rates for testicular cancer in this step affects all subsequent calculations as well. However, using these figures seems justifiable since screening programmes are unlikely to substantially affect the observed incidence of testicular cancer, particularly since they do not prevent the development of testicular cancer and since its rapid growth [53] and typically extracorporeal location suggest a comparatively small pool of latent cases which might be additionally discovered through screening. Calculations based on data from Geczi et al. likewise showed that 763 of 991 men with worrisome TSEs (77%) have testicular abnormalities, and more extensive urological evaluation is required in 39 of them (5%). In 13 of these 39 cases (33%), the examination leads to a suspicion of cancer, resulting in testicular exploration or removal; in 2 cases, the testicular exploration or removal ultimately reveals benign findings and might therefore be deemed unnecessary. The quantity of unnecessary testicular explorations is calculated by multiplying the 13 cases of suspected cancer requiring invasive diagnostic evaluation by Geczi's reported proportion of suspected tumour cases not confirmed by testicular exploration (5/31). For the clinical screening for testicular cancer, data from Roemer et al. [42] allow estimating that testicular abnormalities will be found in 1700 of 100 000 screening participants (1.7%), and more extensive urological evaluations will be required in 200 cases (12%). The actual case numbers in this area are likely even higher since, in light of missing data, it was not possible to include clinical examinations performed due to changes found by the patient in the estimate. The number of necessary and unnecessary testicular explorations/removals as well as the resulting sum of surgical procedures can be estimated based on the range of PPVs of 33–88% (Table 3) [37,41], which were extracted as part of the supplementary presentation, and the incidence of testicular cancer (11/100 000) observed in Germany. The estimate suggests that for every 100 000 men participating in clinical screening, approximately 12–33 testicular explorations/removals can be expected, of which 1–22 will reveal benign findings and might therefore be deemed unnecessary. The estimate of 22 unnecessary procedures is based on the predictive value reported by Peterson [41]. Since this was the only study conducted in asymptomatic men, an estimate based on its data possesses higher credibility. Despite the lack of comparison with the current no-screening situation, the estimate shown in the flow chart reveals that, in case of TSE-based screening, no more than negligible added harm in the form of unnecessary testicular exploration would be expected; this harm could be offset or outweighed even by slight gains in benefits. Recommendations in favour of regular TSE, such as from the German Society of Urology, the German Cancer Society, and the Federal Centre for Health Education [54–56], appear to adopt this perspective, despite the lack of scientific evidence of benefit. However, it should also be noted that even TSE-based screening can lead to the consumption of additional medical resources for the diagnostic evaluation of suspected cases or as a result of testicular abnormalities, which are often discovered upon

targeted examination. As illustrated by the estimate in the flow diagram, clinical screening would be expected to be many times more resource-intensive than TSE. Furthermore, there would be a risk of a substantial increase in unnecessary testicular exploration, representing harm which would need to be balanced out by higher gains on the benefit side.

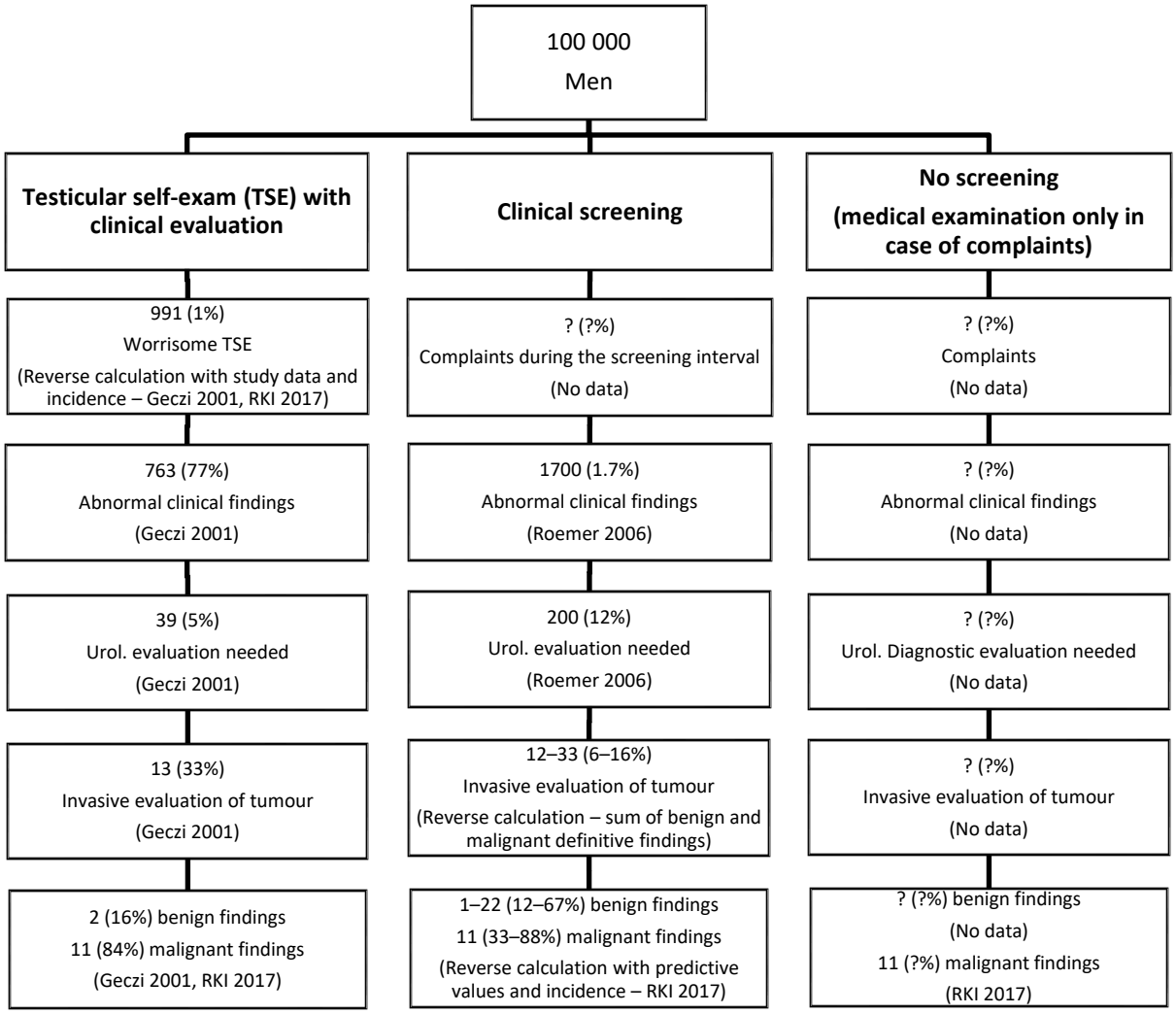

Figure 2: Flow diagram for estimating the harm from testicular cancer screening

RKI: Robert Koch Institute

The presented calculations exhibit a series of fundamental limitations:

1. Even on the basis of the data from the supplementary presentations, it is not possible to draw any comparative conclusions on the potential benefit and harm of the three options – namely no screening (or clinical palpation of the testis upon request from the 45th year of life), screening by TSE, and screening by clinical palpation and scrotal ultrasound – because no data

on benefits (prevented deaths, prevented cases of metastatic testicular cancer) were available or derivable for the screening situation and no data on harm (cases with unnecessary testicular exploration or removal) were available or derivable for the no-screening status quo. In principle, differences in quality of life resulting from the prevention of advanced cancer stages, burdensome treatment forms, and their late toxicities should be included in the comparison as well. Due to the lack of available evidence, this was impossible to do.

2. The assumptions made regarding the PPVs for clinical examination are largely from diagnostic studies with preselected patients rather than from a population of asymptomatic men, as would be the case in a clinical screening exam. This typically leads to overestimates of the PPV when compared with an unselected population and hence to underestimates of the potential harm. No systematic assessment of the studies' risk of bias was carried out, and therefore, any further potential weaknesses of the studies were not included in the assessment.

3. The assumptions made on stage distribution at the time of diagnosis and on stage-specific survival rates are based on registry data of limited quality: In up to 30% of data, staging information may be missing [47]. Only a small proportion of registry data are from Germany. However, 82% of the 12 881 included cases are from the Netherlands, Austria, Norway, Germany, and Switzerland and hence from countries with similar living conditions and health systems.

4. The calculation of benefit and harm required assumptions reflecting the actual situation to an unknown or only limited extent. For instance, it was assumed that screening could discover all metastatic tumours in the local or regional stage. Most assumptions were made in such a way that the potential bias would be in favour of the effectiveness of screening.

6 Results: Health economic assessment

6.1 Intervention costs

Since the lack of data precludes an estimate of the costs of a potential screening programme, they are not presented in this HTA report. The only available cost data are the fees of examinations in the current situation with testicular cancer screening from the 45th year of life, but they would represent only some components of a more comprehensive testicular cancer screening programme.

TSE is not associated with any direct costs. However, the average cost of TSE per person including clinical diagnostic evaluation cannot be calculated, since no data are available for estimating the prevalence of suspected testicular cancer or the utilization of diagnostic evaluations. The same is true for the frequency at which individual diagnostic steps would be taken based on the respective interim findings (e.g. testicular exploration); therefore, it was impossible to include and calculate the cost of false-positive findings.

No data are available on the prevalence of therapeutic measures resulting from screening. Prevalence data are also missing for calculating the cost of a screening programme conducted using clinical palpation and scrotal ultrasound. In this case, additional costs would be incurred due to the establishment and quality assurance of an organized screening programme with an invitation system, obtaining informed consent, and quality assurance. The aforementioned measures are required by law for cancer screening programmes under the European guideline for quality assurance (SGB V, Section 25a) [57].

In the current reimbursement situation, a urological evaluation due to possible disease being suspected after TSE costs EUR15.48 for the clinical examination, EBM code 1731 “cancer screening in men” plus EUR9.42 for the ultrasound, EBM code 33043, “33043 B-mode ultrasound examination of one or more genitourinary organs”.

6.2 Cost effectiveness

The information retrieval found no systematic reviews and no cost effectiveness studies meeting the inclusion criteria.

The search strategies for bibliographic databases are found in the appendix. The most recent search was conducted on 7 November 2018.

6.2.1 Results on cost effectiveness

No suitable studies to assess the cost effectiveness of testicular cancer screening were available.

However, a study by Aberger et al. [21] was deemed to be additional literature of interest. This cost study conducted in the U.S. healthcare system compared the cost of an advanced-stage testicular tumour versus the cost of earlier tumour stages or benign changes detected through TSE. It showed that the cost for an advanced-stage testicular tumour was 2–3 times higher than that for a tumour detected in an early stage or 313–330 times more than the cost of clinically evaluating a benign change. The authors conclude that the possible savings from preventing advanced stages might exceed the cost of unnecessary clinical evaluations due to TSE.

6.2.2 Discussion

The literature search did not find any health economic evaluations comparing the added cost of testicular cancer screening with its added benefit in comparison with the no-screening situation. The U.S. study by Aberger et al. [21], which was included in the present HTA report as additional literature of interest, refers to the USPSTF argument of unproven benefit by noting that screening might eliminate some costs.

Due to the cost of testicular cancer cases detected early being 2–3 times lower, the authors conclude that the potential savings from the prevention of cases discovered in an advanced stage might exceed the cost arising from unnecessary clinical evaluations associated with TSE. Since the amount by which unnecessary examinations and testicular explorations would increase with TSE screening in comparison with a no-screening situation is unknown, there is no way to determine how many advanced-stage cases would actually need to be prevented to save costs. Based on the estimate shown in Figure 2 of this HTA report, TSE-based screening is likely to result in 28 unnecessary extensive urological evaluations per 100 000 men (39 urological evaluations – 11 confirmed testicular tumours = 28), of which 2 include unnecessary testicular exploration or removal. On the basis of the data reported by Aberger et al. [21], the cost of unnecessary urological evaluations per 100 000 men was $31 500. Under the worst-case assumption from the screening perspective, namely that all unnecessary examinations result from TSE, about 1 advanced testicular tumour would have to be detected in an earlier stage per 100 000 men in order to compensate the cost (cost savings of approx. $28 500 per case). This would approximately equal the previously estimated maximum number of metastatic testicular tumours which are potentially avoidable by screening (see Figure 1). For clinical screening, the calculations are even less favourable: The number of unnecessary urological evaluations would equal 189 (200 – 11 confirmed testicular tumours = 189). These additional costs would be impossible to offset. In general, it must be noted that transferring U.S. cost data to the German healthcare context, as was done in this case, is best done only to provide a general idea of relative magnitudes.

7 Results: Social, ethical, legal, and organizational aspects

7.1 Results on social aspects

The scoping search or use of the literature from the searches for the benefit assessment and health economic assessment domains identified 27 studies (22 cross-sectional studies [58–79] and 5 interventional studies [80–84]) with some 7800 study participants.

In addition, 6 interviews were conducted with potentially affected persons, and relevant passages of the interview were transcribed and entered into an extraction table based on the topics of the interview guide.

This section focuses on analysing social and sociocultural aspects concerning TSE in men at average risk of testicular cancer since the scoping search found a wealth of information on this topic. Whenever available, aspects of clinical examination and scrotal ultrasound were addressed in the results (e.g. aspects of testicular cancer education).

The identified studies were conducted in the United States (2 interventional studies, 7 cross-sectional studies), United Kingdom (1 interventional study, 6 cross-sectional studies), Ireland (2 cross-sectional studies), Portugal (1 cross-sectional study), Sweden (2 cross-sectional studies), and Turkey (2 interventional studies, 4 cross-sectional studies). The study population comprised pupils, boy scouts, students (college or university), civil servants, employees of public universities, bank employees, employees of industrial companies, nursing staff, soldiers as well as patients of general practitioners and of a genitourinary medicine clinic. The number of included study participants ranged from 20 to 799 men, and the mean age of surveyed men was between 15 and 44 years. Data collection instruments included standardized questionnaires (e.g. Health Belief Model), self-constructed questionnaires, interviews, and focus group discussions.

As to level of knowledge, the various studies consistently showed a relatively low health literacy level in the male population regarding both testicular cancer and TSE. The majority of the surveyed men had heard of testicular cancer and/or TSE before, but few of them had received more detailed information (e.g. on associated symptoms, age ranges at highest risk of testicular cancer, how and when to perform TSE / what to feel for) or training (for TSE) [58,59,63–65,68–74,77,78,80–83]. The exception were surveyed male junior physicians as well as men treated at a genitourinary medicine clinic.

Lack of knowledge was frequently cited by the surveyed men as a reason for not practising TSE [68,69,71,77,81], with the frequency of this aspect being cited being between 50% [81] and 88% [71]. Additionally, in some studies, knowledge or absence thereof was a significant factor influencing whether TSE was practised or not [63,69,71,72]. Men who had been informed about TSE and its advantages or were trained on how to perform TSE were

significantly more likely to practice TSE [62,63,68,69,73]. In addition, men felt prepared to perform TSE after they had been instructed (e.g. by healthcare staff) on how to perform TSE and what to watch out for [73]. On the basis of the identified studies or interviews with affected people, it was also found that men do in fact welcome information about testicular cancer and TSE. It was important to the men that the information be presented in a patient-oriented manner, that medical language be adapted to the patient's questions, and that appealing media be used [63–68,72,77]; (interviews with affected people).

The studies which investigated the ways through which men obtain information about testicular cancer or TSE showed social media in first place (some 60–70%) [59,65,66,70,74,77]. Few of the surveyed pupils and students cited consultation of a general practitioner or information materials or campaigns found in doctor's offices as their sources of information on testicular cancer and/or TSE (2% to 32%) [59,65,66,70,71,74]. Exceptions were attributable to the setting or the included study population. For instance, men treated at a genitourinary medicine clinic cited the treating physician or healthcare staff as the main source of information (74%), while media were rarely mentioned (3%) [68].

Interviewed patients also mentioned that the information should come from a reliable, trustworthy source, referring to both public healthcare facilities and healthcare staff.

With regard to psychosocial factors associated with TSE, 1 interventional study (n = 174, Turkey) and 4 cross-sectional studies (total n = 1851; United Kingdom, Turkey) cited fear of finding abnormalities in TSE as a reason for not performing it, albeit this occurred only rarely and to a small extent (between 2% and 15%, with the highest value coming from men surveyed at a genitourinary medicine clinic [68,69,71,77,81]). Men who worry about testicular cancer tend to practice TSE more frequently (1 cross-sectional study from the United Kingdom, n = 188) [62].

The sense that performing TSE is sinful or feelings of guilt or shame associated with TSE were cited as reasons for not practising it by 1 interventional study (n = 174; Turkey) and 4 cross-sectional studies (total n = 1691; United Kingdom, Turkey), with the frequency at which it was cited being relatively homogeneous, between 2% and 6% [68,69,76,77,81].

In 2 cross-sectional studies (total n=415, United Kingdom, United States), a sense of relief when not finding any abnormalities during the TSE as well as a sense of control are described as factors potentially influencing the performance of TSE and motivating factors for practising it in future [72,76].

With regard to sociodemographic differences, 2 cross-sectional studies from the United Kingdom (n = 202) and the United States (n = 213) suggested that there are differences between population groups of different ethnic backgrounds in terms of how frequently TSE

was performed, with white men being more likely to practise TSE [69,78]. With regard to age, 3 cross-sectional studies showed heterogeneous results regarding the relationship between practising TSE and the person's age (total n = 1619; Ireland, United Kingdom). A cross-sectional study (n=191, United States) showed that lack of educational qualifications, frequent family problems as well as lack of social support can be further factors for less frequent performance of TSE [79].

7.2 Results on ethical aspects

In the scoping search, no publications specifically investigating ethical aspects of testicular cancer screening were found. One publication contained an explicitly ethically justified recommendation in favour of TSE [85]. However, 19 publications investigating ethical aspects of cancer screening in general were included [25,85–102]. They were used to further specify criteria of the normative framework on ethical aspects of public health measures by Marckmann [25] for cancer screening (see Table 25 of the full report). These criteria serve as the basis for the analysis of the ethical aspects of testicular cancer screening programmes.

In addition, 6 interviews were conducted with members of the target group, and relevant interview passages were transcribed and entered into an extraction table, thematically organized based on the interview guide. Relevant statements were included in the ethical evaluation of testicular cancer screening.

Ethical questions arose in the application of ethical requirements, particularly due to the lack of direct evidence from studies of high methodological quality. No relevant conflicts between the various ethical requirements were identified.

Expected health benefit for the target population

The results of the benefit assessment were used for the ethical evaluation of the expected health benefit. Accordingly, the incidence of testicular cancer, at 11 malignant tumours and 0.4 deaths per 100 000 men per year and a total of 153 deaths per year [1], is much lower than, for instance, the incidence of colon cancer (83 cases with 34 deaths per 100 000 men per year; total of 13 580 deaths per year [1]). While testicular cancer is the most common cancer in young men, other causes of death, e.g. suicide (1901 deaths per year), traffic accidents (1014 deaths per year), and heart attacks (453 deaths per year) are far more common in this age group [103]. Although there is no generally accepted measure for the relevance of a health problem, testicular cancer seems to be of lesser relevance in terms of its prevalence and mortality when compared with other cancers and other causes of death. In addition, 80% of patients discover testicular cancer in a local or regional stage, in which it is associated with a comparatively good prognosis (relative 5-year survival rates of 96–99%). Due to lack of evidence, it is unclear how many of the advanced cases of testicular cancer might be detectable at an earlier, local stage by means of screening. No valid data on asymptomatic

populations are available for either TSE or clinical examination (see Section 5.1). However, the test methods themselves are known to be safe.

For testicular cancer, comparatively effective treatment options with good 5-year relative survival rates are available (see Sections 1.2 and 5.2). No data are available to determine whether it is possible to further improve treatment outcomes via testicular cancer screening. Due to the comparatively favourable stage distribution and treatment effectiveness in self-detected testicular cancer, however, no major improvements can be expected. At most 0.7 to 1.2 metastatic cases out of a total of 11 cases per 100 000 persons could theoretically be detected in earlier stages. Whether testicular cancer screening can reduce all-cause mortality in the target population is unclear due to a lack of evidence. At most 153 out of a total of 450 000 deaths could theoretically be reduced annually if all testicular cancer deaths were preventable by screening measures. No data are available on the reduction of cancer-specific mortality either. At 11 disease cases per 100 000 persons per year, a maximum reduction by 0.4 deaths would be possible if all testicular cancer cases were preventable by screening measures. Gains in quality of life through the prevention of advanced tumour stages, more burdensome forms of therapy, and their late toxicities seem plausible, but no empirical evidence with comparative data on health-related quality of life for various stages of disease is available.

Due to a lack of evidence, it is unclear whether there are any favourable effects resulting from incidental findings. Analytically, this does seem rather unlikely, however, since the expected incidental findings, e.g. spermatoceles, hydrocoeles, hydatides, or epididymal dissociations, are largely benign and very rarely require treatment or would be detected even without screening. Given younger men's currently limited awareness of the risk of testicular cancer, worries about the risk of testicular cancer are likely not widespread, and therefore, any potential positive psychological effects are likely small.

Overall, no conclusion on the benefit of testicular cancer screening can be drawn due to a lack of controlled interventional studies. However, the epidemiological data for estimating the maximum theoretically possible benefit of testicular cancer screening are plausible; new data therefore seem unlikely to substantially change the evaluation.

Potential harm and burden

No comparative studies are available on the burdens and risks associated with regular testicular cancer screening measures in asymptomatic young men. Analytically, any direct risks are deemed low since palpation and ultrasound involve no physical risks. Clinical palpation might possibly be experienced as uncomfortable, but according to the interviews, this is unlikely. Risks from false-positive findings are also difficult to assess. In preselected populations, TSE is associated with unnecessary testicular exploration or removal in the

further evaluation in 16% of cases, while for clinical screening, this is true in 12–67% of cases (1–22 per 100 000). Testicular exploration is typically not associated with any long-term effects, and in case of orchiectomy, fertility is typically preserved. False-negative results are rare in the preselected populations (high sensitivity), but evaluation bias must be taken into account since negative findings are not evaluated invasively. Since testicular cancer typically grows rapidly, further evaluation by watching the clinical course might be sufficient. There is no evidence on the risks of overdiagnosis and overtreatment, but the rapid growth of testicular tumours makes a high risk of overdiagnosis and overtreatment unlikely.

No data from Germany are available on potential adverse psychological effects. In 5 studies from Turkey and the United Kingdom, anxiety and worries were cited as potential reasons for not practising TSE in a small percentage of participants (2–15%). Additionally, screening measures could lead to worries and an impaired sense of wellbeing due to greater awareness of the risk of testicular cancer. Adverse psychological effects from incidental findings are conceivable if further evaluations worry the patient.

Overall, due to a lack of high-quality studies, the strength of evidence for potential harm is deemed low.

Effects on autonomy

Due to the lack of direct evidence on the expected benefit and harm, the ability of potential participants to make informed decisions regarding testicular cancer screening is limited. In the above-mentioned studies from Turkey and the United Kingdom, a few participants (2–6%) reported feelings of shame during TSE; depending on cultural background, this aspect might require consideration in education on testicular cancer screening. No evidence-based recommendation regarding testicular cancer screening on the basis of a valid, empirical benefit-harm analysis in comparison with the status quo can be made. However, reasonably reliable evidence on the relatively small maximum possible added benefit of testicular cancer screening can be inferred from epidemiological data (prevalence of disease, stage distribution at initial diagnosis, stage-specific prognosis), at least with regard to a theoretically possible reduction in cancer-specific mortality. No comparable data are available regarding potential gains in quality of life. The confidentiality of test results would need to be assured, particularly with regard to emotionally delicate consequences of the disease, such as reduced fertility.

Justice-related implications

Given the current evidence, justice-related implications of testicular cancer screening seem to be less relevant. If the benefit–harm relationship were in favour of testicular cancer screening, the screening and the corresponding information would have to be made available to all men. In particular, any inequalities due to socioeconomic status and age would have to be taken into account. According to 2 cross-sectional studies from the United Kingdom and the United

States, ethnic background may influence the frequency at which TSE is practised (white men tend to perform it more frequently). According to 1 U.S. cross-sectional study, lack of school qualifications, frequent family problems, and lack of social support can be influencing factors leading to less frequent practise of TSE. Three cross-sectional studies from Ireland and the United Kingdom failed to show a consistent relationship between TSE performance and participant age.

There is no evidence suggesting any specific unequal distribution of the potential benefit and harm of testicular cancer screening. Likewise, there is no evidence suggesting that specific effects on health-related inequities are to be expected.

Expected efficiency

Due to a lack of studies, the benefit–harm relationship of testicular cancer screening cannot be empirically assessed. Cost savings are rather unlikely given the comparatively low incidence of testicular cancer and the low expected added benefit from testicular cancer screening due to 5-year survival rates already being high in the absence of testicular cancer screening. No conclusions can be drawn on whether acceptable cost effectiveness is achievable in the German healthcare system.

Effects on perception of disease and health behaviours

No empirical evidence is available on any effects of testicular cancer screening on perception of disease and health behaviours. However, young men's perception of disease might conceivably change if they were more aware of the risk of testicular cancer as a result of testicular cancer screening. Testicular cancer screening is not expected to promote higher-risk lifestyles since lifestyle is not known to impact disease development.

Synthesis: Comprehensive ethical assessment and recommendation

Overall, an empirical estimate of the potential benefit and harm of testicular cancer screening is possible only to a limited extent or not at all due to lack of evidence. On account of the comparatively low incidence and good prognosis of testicular cancer even in the absence of screening, the added benefit of testicular cancer screening is likely low, however, particularly if compared with other cancers, like colon cancer. Testicular cancer screening itself is not associated with any direct physical risks or burdens. From other cultures, there were few reports of potential psychological burdens due to a sense of shame associated with TSE or clinical testicular examination. The potential harms arising from unnecessary testicular exploration or removal as part of the evaluation of abnormal findings must be taken into account. Given that any potential benefit comes without empirical evidence and has been analytically assessed to be relatively small and that potential harm can be expected at the same time, general testicular screening, whether via TSE or via clinical exams, cannot be recommended from an ethical perspective. When viewed in conjunction with the fact that

resource use is difficult to justify, clinical testicular cancer screening should be offered neither as a standard SHI benefit nor as an individual out-of-pocket health service (*Individuelle Gesundheitsleistung*, IGeL) To the extent that young men would like to regularly practise TSE on their own initiative, this seems more justifiable because of the likely lower potential harm, so long as they are (1) informed about the lack of direct evidence and the analytical estimates of the potential benefit and harm of testicular cancer screening and (2) are instructed on how to perform the TSE. In populations at higher risk of testicular cancer, a more favourable benefit–harm balance would be expected. However, no interventional studies are available on testicular cancer screening in high-risk populations.

Due to the low incidence of testicular cancer, it would be very resource-intensive to conduct controlled studies of high methodological quality to generate the missing evidence on potential benefit and harm. Since most cases of testicular cancer are detected at an early stage – even without screening – and can be treated with a good prognosis, the question arises whether it is justifiable to spend the considerable resources required to conduct studies of high methodological quality to investigate the potential benefit and harm of testicular cancer screening. At most, an evaluation of testicular cancer screening in populations at elevated risk of testicular cancer might be contemplated. Such evaluation should also survey comparative data on health-related quality of life in various phases of disease.

7.3 Results on legal aspects

The relevant laws of SGB V [57] and its implementing ordinances were used rather than conducting a separate literature search on legal aspects.

Services covered by the SHI

SGB V Chapter Four governing benefits for identifying health risks and screening for diseases, particularly Sections 25 and 25a on health examinations and organized screening programmes, were identified as relevant legal texts, as were the G-BA Rules of Procedure [104], which discuss the implementation of screening programme assessment in more detail. In addition, the G-BA's cancer screening guideline, which describes the cancer screening measures included in the SHI catalogue of services, was taken into account [105]. In terms of screening measures for men from age 45 years, it lists the inspection and palpation of the external genitals, including the corresponding skin areas.

Criteria for assessing screening exams

SGB V, Section 25(3) lists the criteria to be used to assess screening exams:

"A prerequisite for the examination.... is that the disease can be effectively treated... The measures taken as part of the screening further require that (1) the preliminary and early stages of disease can be detected by diagnostic measures, (2) the signs of disease can be

unequivocally measured by means of medical technology, and (3) sufficient numbers of physicians and facilities are available to definitively diagnose and treat the identified suspected cases. Insofar as its consultations about a health examination as per Section 1 prompt the G-BA to determine that necessary information is missing, the G-BA may decide on a guideline for testing the suitable technical and organizational design of the health examination"[104].

Suitable evidence for evaluating the assessment criteria

The Rules of Procedure Chapter 2, Sections 10–11 contain the relevant provisions for evaluating screening exams with regard to the various criteria for study types to be used and the evidence hierarchy. Section 13 contains provisions concerning the overall evaluation in the context of care [104]. Section 13 (1) states: "Before the decision is made in accordance with Section 15(1), a comprehensive weighing process must take place, taking into account the scientific evidence, particularly the documents analysed in accordance with evidence criteria." Section 13(2) states that, generally, evidence class I, i.e. systematic reviews of randomized clinical studies with patient-related outcomes (mortality, morbidity, quality of life), is to be used as qualitatively appropriate documents for weighing benefit and harm. If demanding this evidence level would be inappropriate due to specific circumstances, lower evidence levels may be used. "However, for patient protection purposes, the recognition of a method's medical benefit based on documents of a lower evidence level requires justification – also taking into account medical necessity – more so the further it departs from evidence level I. For this purpose, the potential benefit of a method must be weighed particularly against the risks of use in patients if the associated evidence of effectiveness is of lesser informative value." [104]

Assessment of medical necessity

Section 3 covers the assessment of medical necessity. "Medical necessity is assessed in the context of care, taking into account the relevance of the medical problem, the course and treatability of the disease, and particularly the diagnostic and therapeutic alternatives already established in SHI care. This is in part gauged by the achieved or hoped-for improvement of care received through the SHI (...)" [104].

Services outside the SHI

Many screening examinations are also offered by specialists in the form of individual out-of-pocket health services, so-called IGeL [106–108]. These services are not listed in the defined SHI catalogue of services, and their costs are therefore not covered by SHI. Unlike measures included in the SHI catalogue of services, IGeL require a prior written agreement to ensure that the physician has complied with his or her duty to inform the patient. Since SHI patients are typically treated on the basis of the benefit-in-kind principle after merely presenting their insurance card and therefore potentially fail to develop sufficient awareness of medical

services requiring payment, the Federal Master Treaty for Medical Practitioners (*Bundesmantelvertrag für Ärzte*) requires that the patient be informed about the financial consequences of private care. The physician is paid by the patient directly, and billing must follow the German medical fee schedule (GOÄ). The GOÄ is typically used for billing services within the private health insurance system.

In this report, the specifications of the Rules of Procedure were operationalized in the methods sections of the benefit assessment and cost effectiveness assessment. Furthermore, sociopsychological and ethical aspects were included in the assessment. In the present case, the assessment of medical necessity in the healthcare context based on the relevance of the medical problem and the course and treatability of the disease seems to be a particularly important criterion for deciding whether future research on testicular cancer screening is recommended.

7.4 Results on organizational aspects

Given the fact that there is no proof of added benefit regarding the investigated testicular cancer screening measures, it seems unnecessary to perform an extensive search for literature on the organization of early detection measures. Sources used were a publication on criteria for the introduction of screening authored by Wilson and Jungner for the WHO [29], a UK NSC publication [30], and the book “Screening. Evidence and Practice” by Raffle and Gray [31]. Gray oversaw the introduction of organized screening programmes in the United Kingdom and was UK NSC programme director.

As early as in 1968, the WHO established criteria defining when it makes sense to introduce screening programmes [29]. These criteria are still in frequent use and have been further developed, e.g. by the UK NSC in the United Kingdom, also regarding the organizational implementation of screening programmes [30].

In accordance with one of the UK NSC criteria, screening programmes should be introduced only if evidence is available from randomized studies showing that they can effectively reduce mortality and morbidity. The criteria also require that, before a screening programme is introduced, treatment be optimized by service providers and any other potentially more cost-effective measures always be reviewed. If there is sufficient evidence of benefit outweighing harm, the criteria call for systematic planning, implementation, and quality assurance of the introduction of screening programmes to ensure that a favourable benefit–harm balance is achieved in practice [30].

If no evidence of a favourable benefit–harm balance is available, and instead, the evidence suggests little potential benefit, conducting testicular cancer screening would be inappropriate. Raffle and Gray [31] (pp. 209–220) advocate against performing inappropriate screening so as to prevent poor practices from becoming established and their later

elimination being viewed as a cost-cutting measure. After analysing the reasons why people or certain groups desire screening, it is recommended to compile information materials which bring into context all important aspects of what should be done to improve the prevention, treatment, and care provision of a specific disease. Potential benefits and harms as well as resources needed for screening should be specifically quantified within this context, and a sound justification of why screening is of lesser benefit should be provided. Further, the information should be adapted to the respective target audience (e.g. health policy decision makers, healthcare organizations, media, public). Armed with these materials, one could then approach persons who call for screening programmes and, for instance, attend interest group meetings in order to start a dialogue with affected people. This might convince them that screening would be the wrong approach in that particular case.

If such fairly informal measures seem insufficient, Raffle and Gray recommend that health policy decision makers develop guidelines which can serve as control measures for curbing the development of inappropriate screening measures. Key stakeholders, e.g. general practitioners, clinicians, benefit recipients, and managers, ought to be included in the planning and introduction of a control process, and the introduction and implementation of the control measure properly prepared.

7.5 Discussion

7.5.1 Social and sociocultural aspects

- There are numerous references to social and ethical aspects of interventions. Therefore, 2 complementary approaches were used for this report. To analyse social and sociocultural aspects, empirical results from studies were compiled into content categories and then processed, while ethical aspects were analytically processed (see Section 3.4). Ethically relevant results from the social and sociocultural realm were resorted to as well.

To identify evidence on social and sociocultural aspects, a scoping search specifically for suitable evidence was carried out and terminated as soon as the necessary information was found. Since numerous relevant studies were found in the first search step, the search was not refined further. Therefore, it is conceivable that further studies on the topic, which are not included in this report, exist and might change its results.

The present report is special in that it does not permit to draw any conclusions on the basis of robust evidence on any added benefit of screening by TSE or by clinical palpation and scrotal ultrasound when compared to no screening in asymptomatic men from 16 years of age. However, regarding social or sociocultural aspects, numerous studies on TSE were found, although with methodological limitations. Particularly cross-sectional studies were identified, which recorded and analysed relevant results on the basis of surveys or focus group discussions. The methodological quality of the included studies was not assessed by checklists,

however key study characteristics (e.g. inclusion and exclusion criteria, sample selection, survey tool, analysis method) were recorded and provide some insight on their methodological quality. It was found that the study populations of the cross-sectional studies (except for one small study) were not subject to representative sample selection for the general population of men (e.g. by age or education level). Instead, for instance all male students of a particular university or all male employees of a company were deemed potential study participants and were surveyed, provided they were interested and/or gave consent and met certain inclusion criteria (e.g. defined age range, no diagnosis of testicular cancer). Thus, the results are in part transferable to the corresponding setting, e.g. to university students enrolled in different degree programmes. Moreover, the identified studies comprise heterogeneous study populations. The investigated men were in different settings or phases of life, e.g. school or university students, university employees, practising physicians, other workers, or patients of a general practitioner or a genitourinary medicine clinic. Accordingly, the age of the surveyed men differs between studies, with mean ages having a relatively wide span from 15 to 44 years. None of the studies were conducted in Germany. The studies are predominantly from the United States (9 studies), the United Kingdom (7 studies), and Turkey (6 studies).

With regard to the number of included study participants, the studies ranged from 20 to some 800 surveyed men.

The studies differed substantially in terms of the applied survey instruments, using standardized or self-developed questionnaires as well as interviews or focus group discussions. The defined response categories or aspects to be investigated differ in some cases. To process results of the included studies, the answers were therefore assigned to the above-mentioned categories and summarized accordingly. However, in some cases, this precluded the explicit presentation of detailed results or additional information, and some overlap of results in the categories was possible.

The presented study results must be interpreted in view of these methodological limitations.

Across the various study populations and countries, the male population possessed little knowledge of testicular cancer or TSE – a fact which likely influences the low prevalence of TSE. Surveyed men who were informed about TSE and its advantages or instructed on how to perform it, practised it more frequently. With regard to information on testicular cancer and TSE, the surveyed men in the studies or patient interviews stated that they would welcome “modern”, appealing information channels and targeted contents from trustworthy sources, e.g. public institutions or healthcare staff.

With regard to TSE-related psychosocial factors, a potentially adverse psychological effect is fear or worries caused by practising TSE. The identified studies showed that the fear of finding

an abnormality in TSE was in fact cited as a reason for not conducting TSE, albeit this occurred only rarely or to a small extent. Hence, the available studies cannot be used to justify not educating men about TSE due to potential anxiety, nor can they be used to justify educating them for reassurance purposes.

Notably, in some studies conducted in Turkey and the United Kingdom, a sense of sinfulness or guilt and shame were cited as reasons for not performing TSE. Although this raises the question of transferability of results, this aspect might be relevant for Germany's population of Turkish origin and would have to be taken into account if testicular cancer screening were ever recommended.

The studies showed heterogeneous results regarding sociodemographic aspects. Overall, no specific conclusions can therefore be drawn regarding sociodemographic differences in knowledge about testicular cancer or TSE or about the prevalence of TSE.

In summary, the identified studies illuminate key social, sociocultural, and psychosocial aspects. Due to the described methodological or content-related limitations, however, these results are not fully transferable to Germany or can only suggest potential influencing factors and impacts.

7.5.2 Ethical aspects

The scoping literature search did not identify any scientific publications which investigated the ethical aspects of testicular cancer screening. Hence, the ethical aspects of testicular cancer screening had to be assessed based on an established normative framework for the ethical evaluation of public health measures [25]. The framework was further specified by means of a scoping literature search on ethical aspects of cancer screening in general and supplemented by the further aspect of "effects on health perception and disease behaviour". On the basis of this specified normative framework, the individual ethical aspects of testicular cancer screening were identified and assessed (see Table 25 of the full report).

The fact that studies were missing in many areas also complicated the ethical evaluation of testicular cancer screening. Only the maximum achievable added benefit can be indirectly estimated from epidemiological studies. In addition, this raises the question of which recommendations can be derived from the limited available evidence. In accordance with the internationally established criteria first put forth by Wilson and Jungner for the WHO [29], screening measures should be recommended only (1) if the corresponding disease is an important health problem causing substantial morbidity and mortality and (2) if evidence is available from high-quality, controlled, randomized studies showing that screening reduces mortality and/or increases quality of life. Testicular cancer screening certainly fails to meet the latter criterion. For the first criterion, the challenge is to evaluate whether testicular cancer represents "an important health problem causing substantial morbidity and mortality"

since no generally established evaluation scales exist for this purpose. A comparison with other cancer types and causes of death in young men offers some guidance. It reveals that due the low incidence and good treatability of testicular cancer, e.g. in comparison with colon cancer and other causes of death such as suicide or death from traffic accidents, testicular cancer, represent a less important health problem not associated with “substantial morbidity and mortality”.

An ethical evaluation can result in five different recommendation levels for carrying out public health measures [109]: (1) advise against the measure, (2) measure justifiable if explicitly requested, (3) offer and recommend measure, (4) offer and recommend measure and provide incentives to increase participation rates, and (5) require measure by law. For testicular cancer screening, recommendation levels (3), (4), and (5) are out of the question due to the low theoretically achievable maximum potential benefit, lack of proof from high-quality evidence, and relatively low relevance of the health problem because of high cure rates. Given the potential harm from unnecessary invasive diagnostic evaluation and resource consumption, testicular cancer screening by clinical examination should be advised against (recommendation level 1). However, if explicitly desired by the affected person, TSE appears justifiable in view of its low risk of harm and lower resource consumption, provided it is performed correctly and after the affected person has been educated about the potential benefit and harm associated with it (recommendation level 2). This might particularly apply to men at higher risk of testicular cancer since screening of high-risk populations is typically associated with a more favourable benefit-harm ratio. No interventional studies were found on this topic either, however.

With respect to the suggestion of deriving recommendations on the basis of the analysis of ethical aspects, it is important to keep in mind that value judgements are required – particularly concerning the benefit–harm ratio and the quality of available evidence – for which no scientifically substantiated, generally accepted standards exist. The ultimate decision on whether and in which form to recommend cancer screening must therefore be made by the competent institutions in each healthcare system. In the German SHI system, this decision would be made by the G-BA.

7.5.3 Legal and organizational aspects

The G-BA Rules of Procedure operationalize the statutory requirements for determining when specific screening measures should be included and are allowed to be included in the SHI catalogue of services. The criteria used are congruent with the criteria for sensible screening programmes which have been established internationally for many years, e.g. by the WHO or in the UK healthcare system. A central element is that a favourable benefit–harm balance of screening measures typically must be proven by high-quality, randomized studies. This is not possible for the clinical palpation and scrotal ultrasound investigated in this report. Moreover,

an appreciable unmet need is unlikely to exist given the low demographic relevance of 0.4 deaths per 100 000 men annually, early-stage diagnosis in most cases as well as good treatment options with very high survival rates. Organizational considerations should therefore primarily focus on how to prevent inappropriate screening measures. Clinical palpation of the testis or scrotal ultrasound should therefore be offered neither through the SHI catalogue of services nor as IGeL services.

It is unclear to what extent inappropriate testicular cancer screening is practised in Germany. Websites of several urological practices offer scrotal ultrasound and, in some cases, testicular cancer biomarker tests as individual out-of-pocket health services [110]. In the second half of 2018, the AOK Research Institute (WIdO) surveyed 2007 SHI members from 18 years of age with respect to individual out-of-pocket health services using representative sampling [108]. In the previous 12 months, 28.9% of individuals were offered or billed an individual out-of-pocket health service. At 26.9%, ultrasound was the most common individual out-of-pocket health service. In response to a query, the person in charge of the dataset, lead investigator Klaus Zok, stated that no scrotal ultrasound was reported among the ultrasounds for cancer screening (personal communication with Klaus Zok). Accordingly, it can be assumed that such scans are rarely used, at least by SHI members.

8 Synthesis of results

Neither randomized nor nonrandomized comparative interventional studies investigating the entire screening chain with regard to the benefit of testicular cancer screening were found. For asymptomatic men, there was also no evidence found on the individual screening steps – accuracy of screening test and diagnostic evaluation, benefit of earlier treatment start. Therefore, no evidence-based conclusions can be drawn on any added benefit or harm of screening by TSE or by clinical examination and scrotal ultrasound when compared to no screening in asymptomatic men from 16 years of age. There is no hint of (greater) benefit or (greater) harm. The present report did not explicitly investigate any screening which focused exclusively on men at higher risk of testicular cancer. Our extensive search shows, however, that no interventional studies on the benefit of screening high-risk populations are available either, and hence, no conclusions can be drawn even for this population.

A supplementary presentation using calculations based on epidemiological data from the Robert Koch Institute shows that the maximum theoretically possible added benefit consists of the prevention of 0.4 deaths per 100 000 men annually (153 cases). These calculations assume that all deaths could be prevented by shifting therapy from the advanced stage to a local or regional stage. It is assumed that in 0.7–1.2 testicular cancer cases per 100 000 men annually (267–458 cases), it would be possible to increase the relative 5-year survival rate compared to the average population from 67–81% to 96–99%. No conclusions whatsoever can be drawn on any potential benefit from gains in quality of life as a result of the prevention of advanced tumour stages, more burdensome treatment forms, and their late toxicities because no comparative data on health-related quality of life are available for different disease stages.

PPV calculations from 12 diagnostic studies on the test quality of TSE as well as clinical examination and/or scrotal ultrasound in largely preselected study populations with a total of 7297 patients show that per 100 000 men, clinical examination can be expected to culminate in 1 to 22 cases of unnecessary testicular exploration or removal, while TSE is expected to result in 2 cases. These data are subject to considerable uncertainty because data from preselected study populations are not transferable to asymptomatic men, and data from a study conducted in Hungary cannot be transferred to the German system. The extent of added harm due to testicular cancer screening in comparison with the status quo cannot be estimated even on this basis because missing data preclude a comparison of screening versus the status quo.

It is impossible to estimate the average intervention cost per participant of a potential testicular cancer screening programme with clinical palpation and scrotal ultrasound or with TSE and urological evaluation in case of suspected findings. The same applies to the average cost of the current screening measures for men from 45 years of age. Only the combined cost of the clinical exam and scrotal ultrasound can be determined, at EUR24.90. In terms of

calculating the average costs per participant, data are missing for all options, e.g. on the prevalence of suspected testicular cancer or the utilization of diagnostic evaluation. The same is true for the prevalence of individual diagnostic steps and, for testicular cancer, treatment and follow-up measures based on interim findings (e.g. testicular exploration).

No conclusion on cost effectiveness can be drawn since no studies were found on this topic. However, the alleged cost savings from the lower treatment costs of cases discovered earlier seem rather unlikely to be achieved because the cost of unnecessary clinical evaluations would have to be taken into account as well.

Regarding social and sociocultural aspects, numerous studies (27 in total) were found, conducted in the United States (2 interventional studies, 7 cross-sectional studies), United Kingdom (1 interventional study, 6 cross-sectional studies), Ireland (2 cross-sectional studies), Portugal (1 cross-sectional study), Sweden (2 cross-sectional studies), and Turkey (2 interventional studies, 4 cross-sectional studies) with a total of about 7800 study participants. The investigated men were in different settings or phases of life, e.g. students at school or university, university employees, practising physicians, other workers, or patients of a general practitioner or a genitourinary medicine clinic. The study populations of the cross-sectional studies were not based on a representative sample of the male general population. Most study participants can be assumed to have an average risk of testicular cancer.

Across the various study populations and countries, it was found that the male population possesses little knowledge of testicular cancer and TSE. Lack of knowledge was also frequently cited by the surveyed men as a reason or significant influencing factor for not practising TSE. Surveyed men who were educated about TSE and its advantages and/or were instructed on how to perform it practised TSE more frequently. In the studies and interviews, the respondents expressed a desire for “modern”, appealing information channels and targeted contents from trustworthy sources, such as public institutions or healthcare staff.

With regard to psychosocial factors associated with TSE, the identified studies did cite the fear of finding abnormalities during the examination as a reason for not carrying it out, albeit this occurred only rarely and to a small extent. Notably, in some studies conducted in Turkey and the United Kingdom, a sense of sinfulness or guilt and shame were cited as reasons not to practise TSE.

With regard to sociodemographic differences, the studies had heterogeneous results on the relationship between conducting TSE and respondent age. In isolated cases, differences in the prevalence of TSE were found between population groups of different ethnic backgrounds, with white men being more likely to practise TSE.

No publications were found on the ethical implications of testicular cancer screening. While 1 publication explicitly justified a recommendation in favour of TSE using ethical arguments, it did not supply any analysis of the ethical aspects of testicular cancer screening. A scoping literature search on ethical issues related to cancer screening in general was therefore used to develop a specific framework for the ethical evaluation of testicular cancer screening. The results from the other domains were resorted to during application. Overall, due to a lack of evidence, the potential benefit and harm of testicular cancer screening can be empirically estimated only to a very limited extent if at all. On account of the comparatively low incidence and good prognosis of testicular cancer, even in the absence of screening, the added benefit of testicular cancer screening is likely low, particularly when compared with other cancers, such as colon cancer. Testicular cancer screening itself is not associated with any direct physical risks or burdens. However, potential harm due to unnecessary testicular exposure or removal during the diagnostic evaluation of abnormal findings must be taken into account. Due to the lack of evidence, it is difficult for potential participants to make an informed decision. Given the limited estimated potential benefit and the simultaneously expected potential harm, general screening for testicular cancer cannot be recommended from an ethical perspective. Resource consumption is an additional factor for advising against regular clinical examinations. Young men who, of their own initiative, want to carry out testicular cancer screening by TSE should be informed about the available evidence and the analysis of potential benefit and harm of testicular cancer screening and be instructed on how to examine their own testis.

Due to the low incidence of testicular cancer, it would be very resource-intensive to conduct controlled studies of high methodological quality to generate the missing evidence on potential benefit and harm. The fact that, even without screening, most cases of testicular cancer are detected in an early stage and can be treated with a good prognosis raises the question of whether it would be justifiable to spend the considerable resources required to conduct studies of high methodological quality in order to investigate the potential benefit and harm of testicular cancer screening in men at average risk of testicular cancer. Since the benefit of screening measures increases with the risk of developing the disease, such interventional studies should be performed in high-risk groups, if at all.

SGB V Chapter Four, governing benefits for identifying health risks and screening for diseases, and particularly Sections 25 and 25a thereof on health examinations and organized screening programmes were identified as relevant legal texts on screening within SHI [57], as were the G-BA Rules of Procedure [104], which discuss the implementation of screening measure assessment in more detail. The cancer screening guideline, which describes cancer screening measures included in the SHI catalogue of services, was taken into account as well [105]. As a testicular cancer screening measure for men from 45 years of age, it lists inspection and palpation of the external genital, including the corresponding skin areas.

Physicians with SHI contracts may offer screening exams and other services not covered by SHI as so-called IGeL services [107,111]. These services are not covered by the SHI catalogue of services, and their costs are therefore not reimbursed by the SHI. Unlike services listed in the SHI catalogue of services, individual out-of-pocket health services require a prior written agreement, as specified by the Federal Master Treaty for Medical Practitioners (*Bundesmantelvertrag für Ärzte*). This is intended to ensure that the physician has met his or her duty to inform the patient and the patient was made aware of the financial consequences of private treatment. The physician is entitled to receive payment directly from the patient, and billing must follow the German medical fee schedule.

In this report, the methodology specified by the Rules of Procedure was operationalized in the methods sections for the benefit assessment and cost-effectiveness assessment. In the present case, aside from the criteria for weighing benefit versus harm, another particularly important criterion for deciding whether to recommend future research on testicular cancer screening appears to be the evaluation of medical necessity within the context of care provision.

To identify relevant organizational aspects of screening measures, we used the internationally recognized criteria for the assessment and introduction of screening measures as well as the practical guide based on these criteria and on long-standing experience from the UK screening programme [29–31]. In Raffle and Gray [31], we found recommendations on how to curb the performance of inappropriate screening. The authors recommend determining the reasons and motivations for these screening exams in men and involved groups and to acknowledge the underlying desire to improve the patient's situation. They further recommended to compile information materials which connect the dots among all important aspects of what should be done to improve the prevention, therapy, and care provision for the specific disease. According to the authors, the potential benefit and harm as well as resources needed for screening measures should be specifically quantified within this context, and a good justification should be provided of why screening measures are of little benefit. The information should be targeted to the respective audience (e.g. health policy decision makers, healthcare organizations, media, public). These materials could then be used to approach individuals who call for screening programmes and to attend events such as interest group meetings in order to start a dialogue with affected people. This might convince them that screening would be the wrong approach in that particular case. If such fairly informal measures seem insufficient, Raffle and Gray [31] recommend that health policy decision makers develop guidelines which can serve as control measures for curbing the development of inappropriate screening measures. Key stakeholders, e.g. general practitioners, clinicians, benefit recipients, and managers, should be included in the planning and introduction of a control process, and the introduction and implementation of the control measure should be properly prepared.

9 Discussion

9.1 HTA report compared with other publications

The four systematic reviews identified in the literature search for the benefit assessment [15,18,49,50] likewise conclude that no evidence is available on the benefit of testicular cancer screening through either TSE or clinical examination, wherein the clinical examination excluded scrotal ultrasound. The 2011 USPSTF review [49] resulted in an explicit recommendation against (Recommendation D) screening asymptomatic young and adult men [15]. Even though studies are unavailable, the low incidence and good treatment success even in advanced-stage cases provide moderate certainty to the conclusion that screening is of no benefit. Sladden and Dickinson 1998 made a similar argument [50]. Like the present report, these authors calculated the potentially achievable benefit under the most favourable assumptions regarding the screening test and participation. Ultimately, they advised against testicular cancer screening and recommended the use of typical channels of health education to advise men to promptly seek medical help in case of testicular abnormalities. In addition, they pointed out the unnecessary use of resources which could be of greater benefit elsewhere. In view of this situation, the 2011 Cochrane Review likewise questions the conduct of a randomized clinical trial, also pointing out methodological challenges such as likely participant switching between study arms [18].

U.S. proponents of TSE criticize the USPSTF recommendation for presuming with moderate certainty that screening is useless – despite the lack of empirical evidence from studies of high certainty of results (RCTs) [19]. USPSTF recommendations are made in 5 grades:

(A) The USPSTF recommends the service. There is high certainty that the net benefit is substantial.

(B) The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

(C) The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small.

(D) The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

(I) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is either lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined [112].

Rovito et al. call for changing the grade D recommendation against testicular cancer screening via clinical examination or TSE to a grade I recommendation: They cite favourable effects of TSE even beyond the discovery of testicular cancer, such as improved body awareness and health literacy, potentially improved communication with the physician as well as the discovery of other testicular anomalies requiring treatment. In addition, the authors note the conflicting recommendations made by practitioners who advocate for TSE and scholars who advise against it [85]. In fact, this contradiction is also reflected by the current AMWF S3 guidelines on testicular cancer (see Section 9.2).

The patchy data situation demonstrated in the report raises the question of whether further research would be useful and if so, in which parts of the screening chain, i.e. where a benefit and cost-effective use of research resources could be expected. Formally, this could be clarified only by probabilistic value-of-information analysis [113]. Such an analysis has not yet been conducted. Due to the rarity of the disease and the likely small added benefit of screening from a societal perspective, however, it seems to be of little use at this time to conduct a resource-intensive, randomized interventional study along the entire screening chain in men who are at average risk of testicular cancer. Because the benefit of screening measures increases with the risk of developing the disease, such interventional studies should be performed in high-risk groups, if at all.

9.2 HTA report compared with guidelines

The current AWMF S3 guidelines on testicular cancer [12] start off by giving a strong evidence-based recommendation (grade A) against screening for testicular cancer. Literature sources are the Cochrane Review [18] and the USPSTF report [15]. In the terms of the level of evidence, the report cites the lowest level 5, i.e., expert consensus, with 96% consensus among experts. This evidently refers to screening by physicians because later, a consensus-based weak recommendation (grade EK with 96% consensus; “should” wording) is given for self-examination: “Regular testicular self-examination should be recommended particularly to young men since it can lead to early diagnosis” [12]. However, the evidence from the sources used to advise against screening related to both clinical examination and TSE, that is, the same evidence was used to derive a strong non-recommendation in one case but a weak recommendation in favour in the other case, with the former being characterized as an evidence-based recommendation and the latter as consensus-based. At least in the absence of any further explanations, this seems confusing.

The authors of the present report concur with the USPSTF evaluation. In the absence of randomized studies proving a benefit of testicular cancer screening, it is still possible to rely on epidemiological data regarding the incidence and lethality of testicular cancer as well as on registry data regarding stage distribution at the time of initial diagnosis and stage-specific survival rates. This alternative approach permits to conclude with some certainty that the

theoretically possible benefit of testicular cancer screening in men at average risk is so small that it would be difficult to achieve in practice. This applies to both clinical examination and TSE. Further, the assumption that all advanced tumours are identifiable at an earlier stage is unlikely to be met. In addition, very high participation rates would be necessary to ensure that all cases are discovered at an early stage. Such rates are typically not achievable. For skin cancer screening, for instance, 16% of eligible men and 17.9% of eligible women actually participated in 2017 [114]. Due to the low potential harm, TSE as recommended by the S3 guideline seems more justifiable [12].

The discussion during the oral debate revealed that the guideline's recommendation in favour of regular TSE was primarily intended for high-risk groups, a fact which would need to be addressed in case of a guideline update.

9.3 Critical reflection on the approach used

Since it was foreseeable that no adequate evidence on added benefit of testicular cancer screening would be available in the form of randomized studies, we tried to explore at least subordinate aspects of the benefit and harm of screening in men at average risk, first by using a linked-evidence approach [115] and, after the inclusion criteria were not met for this approach, through the supplementary presentation of diagnostic studies on preselected patients and registry studies on stage distribution and stage-specific prognosis.

The presented calculations are subject to a series of fundamental limitations, which are listed in more detail in the discussion on the supplementary presentation of the medical evaluation (see Section 5.4):

- Comparative conclusions on the potential benefit and harm of the investigated testicular cancer screening measures in comparison with the status quo cannot be drawn, even on the basis of the supplementary presentations, because of a complete lack of data for some of the options. Due to the patchy data situation, it was also impossible to take into account any differences in quality of life which might arise from the prevention of advanced tumour stages, burdensome treatment forms, and their late toxicities.
- The calculated number of cases with harm (testicular exploration and removal) due to clinical screening measures is largely based on studies with preselected patients rather than on a population of asymptomatic men, as would be assumed for clinical screening, and is therefore likely an underestimate.
- The assumptions made on stage distribution at the time of diagnosis and on stage-specific survival rates are based on registry data of limited quality:

For the analysis of social or sociocultural aspects, numerous studies on TSE were identified that illustrate important social, sociocultural, and psychosocial aspects. However, the studies

exhibit diverse methodological or content-related limitations. For instance, sample selection was not representative for the male general population, the examined men were in different settings or phases of life, and none of the studies was conducted in Germany. Therefore, the results are not fully transferable to Germany or can merely suggest potential influencing factors as well as effects of TSE.

Deriving recommendations regarding testicular cancer screening from the available evidence requires value judgements for which neither science nor society offer any clearly defined, generally acceptable standards. The question of whether the relatively low potential benefit of testicular cancer screening justifies the potential harm from invasive diagnostic evaluation and the associated resource consumption is of particular relevance in this context. The recommendations suggested in the report are based, in part, on the internationally established criteria first put forth by Wilson and Jungner for the WHO [29]. Accordingly, screening measures should be recommended only if the condition sought is a major health problem with substantial morbidity and mortality and evidence is available from high-quality, controlled, randomized studies showing that the screening reduces mortality and/or increases quality of life. While the latter criterion is certainly not met by testicular cancer screening, the assessment of the importance of the health problem calls for adequate measures of value. In this report, a comparison with the much more common colon cancer and with other causes of death in the same age group provided some orientation for the assessment of the mortality and morbidity associated with testicular cancer.

Irrespective of the above, the question is whether and in which parts of the screening chain further studies for evaluating the screening measures would be helpful. A scientifically sound answer to this question would require a formal value-of-information analysis. However, in light of the comparatively low incidence and good treatability of testicular cancer, the potential benefit to be expected in theory is small. For this reason, conducting randomized interventional studies to determine the effectiveness and efficacy of screening measures (which themselves are associated with some potential harm) in men who are at average risk of developing testicular cancer does not appear to be appropriate at this time. Because the benefit of screening measures increases with the risk of developing the disease, such interventional studies should be performed in high-risk groups, if at all. Other than that, collecting data on other parameters within observational studies (e.g. on the stage distribution at the time of diagnosis of testicular cancer or the favourable or adverse impact of early diagnosis on the quality of life) might contribute to further reducing the uncertainty of the evidence for these factors to guide the decision.

10 Conclusion

Due to a lack of interventional studies on benefit and harm, the question of whether routine screening of asymptomatic men from 16 years of age (at average or higher risk) results in better treatment outcomes in testicular cancer cannot be answered in an evidence-based manner. There is no hint of (greater) benefit or (greater) harm. No studies are available on cost effectiveness.

The theoretical maximum benefit indirectly derived from epidemiological studies in a supplementary presentation for the benefit assessment is relatively small in comparison with other cancers. Testicular cancer is rare, and even in the absence of routine screening, it is discovered in a relatively early stage in most cases and can be treated with correspondingly high cure rates.

Therefore, routine screening for testicular cancer in men from 16 years of age cannot be recommended at this time. This applies to both TSE and clinical palpation / scrotal ultrasound. The low potential benefit is accompanied by potential harm due to unnecessary testicular exploration or removal. Nonmalignant testicular anomalies, which are frequently discovered as a result of targeted examinations, may worry affected men and sometimes involve unnecessary resource consumption. Particularly in case of clinical examinations, it is possible for the expected harm inflicted by additional unnecessary invasive evaluations to outweigh the expected benefit when looking at the entire target population. Therefore, clinical palpation and scrotal ultrasound for screening purposes should be offered neither as a standard SHI benefit nor as an individual out-of-pocket health service. TSE is likely associated with less potential harm. It seems justifiable for young men worried about the risk of testicular cancer – of which there should be few according to psychosocial studies – to regularly practise TSE after they have been educated about the lack of direct evidence on their potential benefit and harm and instructed on how to perform the exam. The use of conventional health education channels to advise men to promptly see a physician for diagnostic evaluation in case of abnormalities of the testis can absolutely be recommended. Further, men should be educated about risk factors for testicular cancer and the generally more favourable benefit–harm ratio of screening for individuals at higher risk.

Given that a relatively low potential benefit is expected due to the comparatively low incidence and often relatively good treatment outlook for testicular cancer, it seems hardly advisable to overcome the lack of evidence by conducting resource-intensive interventional studies of high methodological quality in men at average risk of testicular cancer. Since the benefit of screening measures increases with the risk of developing the disease, such interventional studies should be performed in high-risk groups, if at all.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under

https://www.themencheck-medizin.iqwig.de/de/hta-berichte/28-ht18-01-hodenkrebs-fuehrt-eine-regelmaessige-frueherkennungsuntersuchung-fuer-maenner-ab-16-jahren-zu-besseren-behandlungsergebnissen.145.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [28] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 7 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 7: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.1; Chapter 4
	Supplementary presentation Section 3.2; Chapter 5
Clinical effectiveness (EFF)	**Benefit assessment** Section 3.1; Chapter 4
	Supplementary presentation Section 3.2; Chapter 5
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.3; Chapter 6
Ethical analysis (ETH)	**Ethical aspects** Section 3.4; Section 7.2
Patients and social aspects (SOC)	**Social aspects** Section 3.5; Section 7.1
Legal aspects (LEG)	**Legal aspects** Section 3.5; Section 7.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.5; Section 7.4

Appendix B – Search strategies

B.1 – Searches in bibliographic databases

B.1.1 – Search strategies for the benefit assessment, modelling studies (supplementary presentations) and the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 06, 2018
- Ovid MEDLINE(R) 1946 to October Week 4 2018
- Ovid MEDLINE(R) Daily Update November 06, 2018
- Ovid MEDLINE(R) Epub Ahead of Print November 06, 2018

#	Searches
1	Testicular Neoplasms/
2	"Neoplasms, Germ Cell and Embryonal"/
3	SEMINOMA/
4	GERMINOMA/
5	(((germ* adj1 cell*) or testicular* or testis*) adj1 (cancer* or carcinoma* or tumor* or tumour*)).ti,ab.
6	(nonseminoma* or non-seminoma*).ti,ab.
7	seminoma*.ti,ab.
8	or/1-7
9	Mass Screening/
10	"Early Detection of Cancer"/
11	(screening* or screened*).ti,ab.
12	or/9-11
13	and/8,12
14	13 not (comment or editorial).pt.
15	..l/ 14 yr=1990-Current

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (testicular* [TIAB] OR testis* [TIAB] OR germ cell[TIAB]) AND (cancer* [TIAB] OR carcinoma* [TIAB] OR tumor* [TIAB] OR tumour* [TIAB])
#2	Search nonseminoma* [TIAB] OR non-seminoma* [TIAB]
#3	Search seminoma*[TIAB]
#4	Search #1 OR #2 OR #3
#5	Search screening* [TIAB] OR screened* [TIAB]
#6	Search #4 AND #5
#7	Search #6 NOT Medline [SB]
#8	Search #7 AND 1990:2018 [DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 November 06

#	Searches
1	exp testis tumor/
2	germ cell tumor/
3	non seminomatous germinoma/
4	(((germ* adj1 cell*) or testicular* or testis*) adj1 (cancer* or carcinoma* or tumor* or tumour*)).ti,ab.
5	(nonseminoma* or non-seminoma*).ti,ab.
6	seminoma*.ti,ab.
7	or/1-6
8	exp mass screening/
9	(screening* or screened*).ti,ab.
10	or/8-9
11	and/7,10
12	11 not medline.cr.

#	Searches
13	12 not (exp animal/ not exp humans/)
14	13 not (Conference Abstract or Conference Review or Editorial).pt.
15	..l/ 14 yr=1990-Current

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 11 of 12, November 2018
- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2018

ID	Search
#1	[mh ^"Testicular Neoplasms"]
#2	[mh ^"Neoplasms, Germ Cell and Embryonal"]
#3	[mh ^"SEMINOMA"]
#4	[mh ^"GERMINOMA"]
#5	(((testicular* or testis*) or (germ* near/1 cell*)) near/1 (cancer* or carcinoma* or tumor* or tumour*)):ti,ab
#6	(nonseminoma* or non-seminoma*):ti,ab
#7	seminoma*:ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	[mh ^"Mass Screening"]
#10	[mh ^"Early Detection of Cancer"]
#11	(screening* or screened*):ti,ab
#12	#9 or #10 or #11
#13	#8 and #12 in Cochrane Reviews
#14	#8 and #12 with Publication Year from 1990 to 2018, in Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Testicular Neoplasms
2	MeSH DESCRIPTOR Neoplasms, Germ Cell and Embryonal
3	MeSH DESCRIPTOR Seminoma
4	MeSH DESCRIPTOR Germinoma

Line	Search
5	((testicular* OR testis* OR (germ* AND cell*)) AND (cancer* or carcinoma* or tumor* or tumour*))
6	(nonseminoma* or non-seminoma*)
7	(seminoma*)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	MeSH DESCRIPTOR Mass Screening
10	MeSH DESCRIPTOR Early Detection of Cancer
11	(screening* or screened*)
12	#9 OR #10 OR #11
13	#8 AND #12
14	(#13) FROM 1990 TO 2018
15	(#14) IN HTA FROM 1990 TO 2018

B.1.2 – Search strategies for treatment studies (supplementary presentations)

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 26, 2018
- Ovid MEDLINE(R) 1946 to November Week 3 2018
- Ovid MEDLINE(R) Daily Update November 26, 2018
- Ovid MEDLINE(R) Epub Ahead of Print November 26, 2018

The following filters were adopted:

- Systematic review: Wong [116] – High specificity strategy

#	Searches
1	Testicular Neoplasms/
2	"Neoplasms, Germ Cell and Embryonal"/
3	SEMINOMA/
4	GERMINOMA/
5	(((germ* adj1 cell*) or testicular* or testis*) adj1 (cancer* or carcinoma* or tumor* or tumour*)).ti,ab.
6	(nonseminoma* or non-seminoma*).ti,ab.
7	seminoma*.ti,ab.

#	Searches
8	or/1-7
9	cochrane database of systematic reviews.jn.
10	(search or MEDLINE or systematic review).tw.
11	meta analysis.pt.
12	or/9-11
13	12 not (exp animals/ not humans.sh.)
14	and/8,13
15	14 and (english or german).lg.
16	..l/ 15 yr=1990-Current

2. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews , Issue 11 of 12, November 2018

ID	Search
#1	[mh ^"Testicular Neoplasms"]
#2	[mh ^"Neoplasms, Germ Cell and Embryonal"]
#3	[mh ^"SEMINOMA"]
#4	[mh ^"GERMINOMA"]
#5	(((testicular* or testis*) or (germ* near/1 cell*)) near/1 (cancer* or carcinoma* or tumor* or tumour*)):ti,ab
#6	(nonseminoma* or non-seminoma*):ti,ab
#7	seminoma*:ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7 in Cochrane Reviews

3. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Testicular Neoplasms
2	MeSH DESCRIPTOR Neoplasms, Germ Cell and Embryonal
3	MeSH DESCRIPTOR Seminoma
4	MeSH DESCRIPTOR Germinoma

5	((testicular* OR testis* OR (germ* AND cell*)) AND (cancer* or carcinoma* or tumor* or tumour*))
6	(nonseminoma* or non-seminoma*)
7	(seminoma*)
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) IN HTA
10	(#9) FROM 1990 TO 2018

B.1.3 – Search strategies for diagnostic studies (supplementary presentations)

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 28, 2019,

The following filter was adopted:

- Diagnostic studies: Haynes [117] – Best balance of sensitivity and specificity

#	**Searches**
#	Searches
1	Testicular Neoplasms/
2	"Neoplasms, Germ Cell and Embryonal"/
3	SEMINOMA/
4	GERMINOMA/
5	(((germ* adj1 cell*) or testicular* or testis*) adj1 (cancer* or carcinoma* or tumor* or tumour*)).ti,ab.
6	(nonseminoma* or non-seminoma*).ti,ab.
7	seminoma*.ti,ab.
8	or/1-7
9	Self-Examination/
10	PALPATION/
11	(self adj2 (detection or efficacy or exam*)).ti,ab.
12	palpation.ti,ab.
13	or/9-12
14	Mass Screening/
15	diagnostic imaging.fs.
16	screening*.ti,ab.

#	Searches
17	(ultraso* adj3 scan*).ti,ab.
18	or/14-17
19	8 and (13 or 18)
20	sensitiv:.mp.
21	predictive value:.mp.
22	accurac:.tw.
23	or/20-22
24	and/19,23
25	24 not (exp animals/ not humans.sh.)
26	25 and (english or german).lg.
27	26 not (comment or editorial).pt.
28	..l/ 27 yr=1980-Current

2. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials, Issue 1 of 12, January 2019

ID	Search
ID	Search
#1	[mh ^"Testicular Neoplasms"]
#2	[mh ^"Neoplasms, Germ Cell and Embryonal"]
#3	[mh ^"SEMINOMA"]
#4	[mh ^"GERMINOMA"]
#5	(((testicular* or testis*) or (germ* near/1 cell*)) near/1 (cancer* or carcinoma* or tumor* or tumour*)):ti,ab
#6	(nonseminoma* or non-seminoma*):ti,ab
#7	seminoma*:ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	[mh ^"Self-Examination"]
#10	[mh ^"PALPATION"]
#11	(self NEAR/2 (detection or efficacy or exam*)):ti,ab
#12	palpation:ti,ab
#13	#9 or #10 or #11 or #12
#14	[mh ^"Mass Screening"]

ID	Search
#15	MeSH descriptor: [] explode all trees and with qualifier(s): [diagnostic imaging - DG]
#16	[mh "diagnostic Imaging"]
#17	screening*:ti,ab
#18	(ultraso* NEAR/3 scan*):ti,ab
#19	#14 OR #15 OR #16 OR #17 OR #18
#20	#8 AND (#13 OR #19) with Publication Year from 1980 to 2019, in Trials

B.2 – Searches in study registries

B.2.1 – Benefit assessment

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(nonseminoma OR seminoma OR testicular cancer OR testis cancer OR Men AND Germ Cell Tumor) AND (screening OR screened)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
nonseminoma OR seminoma OR testicular cancer OR testis cancer OR Men AND Germ Cell Tumor

B.2.2 – Diagnostic studies (supplementary presentations)

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(nonseminoma OR non-seminoma OR seminoma OR testicular cancer OR testis cancer OR Men AND Germ Cell Tumor) AND (self examination OR self detection OR self efficacy OR self exam OR palpation OR scan OR screening)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
nonseminoma OR seminoma OR testicular cancer OR testis cancer OR Men AND Germ Cell Tumor