LUNG TRANSPLANT

Surveillance bronchoscopy in children during the first year after lung transplantation: is it worth it?

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Background: Since January 2002, routine surveillance bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy has been performed in all paediatric recipients of lung and heart–lung transplants at the Great Ormond Street Hospital for Children, London, UK, using a newly revised treatment protocol.
Aims: To report the prevalence of rejection and bacterial, viral or fungal pathogens in asymptomatic children and compare this with the prevalence in children with symptoms.
Participants: The study population included all paediatric patients undergoing single lung transplantation (SLTx), double lung transplantation (DLTx) or heart–lung transplantation between January 2002 and December 2005.
Methods: Surveillance bronchoscopies were performed at 1 week, and 1, 3, 6 and 12 months after transplant. Bronchoscopies were classified according to whether subjects had symptoms, defined as the presence of cough, sputum production, dyspnoea, malaise, decrease in lung function or chest radiograph changes.
Results: Results of biopsies and BAL were collected, and procedural complications recorded. 23 lung-transplant operations were performed, 12 DLTx, 10 heart–lung transplants and 1 SLTx (15 female patients). The median (range) age of patients was 14.0 (4.9–17.3) years. 17 patients had cystic fibrosis. 95 surveillance bronchoscopies were performed. Rejection (≥A2) was diagnosed in 4% of biopsies of asymptomatic recipients, and in 12% of biopsies of recipients with symptoms. Potential pathogens were detected in 29% of asymptomatic patients and in 69% of patients with symptoms. The overall diagnostic yield was 35% for asymptomatic children, and 85% for children with symptoms ($p<0.001$). The complication rate for bronchoscopies was 3.2%.
Conclusions: Many children have silent rejection or subclinical infection in the first year after lung transplantation. Routine surveillance bronchoscopy allows detection and targeted treatment of these complications.

Lung transplantation has become an accepted treatment option for end-stage lung disease even in children, but the overall survival remains poorer compared with other solid organ transplants.[1] Most early deaths are related to overwhelming infection in the immunocompromised host, accounting for almost 50% of deaths in the first year after transplant.[2] The International Society of Heart and Lung Transplantation (ISHLT) Eighth Official Registry Report 2005 showed that infection remains a major cause of mortality throughout the entire follow-up period, even if cytomegalovirus (CMV) is excluded. Acute cellular rejection (ACR) accounts for 4% of deaths up to 1 year after transplant, but bronchiolitis obliterans is the major cause of death by 5 years after transplant.[2 3]

Several authors have reported an association between an increased incidence and severity of ACR and the subsequent development of bronchiolitis obliterans; non-alloimmunological factors such as bacterial, viral and fungal infection may also have a role.[4 5] Early detection and treatment of ACR or infection enables prevention of irreversible graft damage, and may therefore have a positive effect on long-term survival after lung transplantation.

Fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy has become the most valuable tool used to monitor the lung transplant recipient and detect ACR and infection. The procedure provides direct visualisation of the airway and anastomoses and the ability to obtain lung tissue and bronchoalveolar specimens, even in the paediatric age group.[6 7]

At the beginning of 2002, our treatment protocols for children who had undergone lung transplantation were revised, and a new triple immunosuppression therapy including tacrolimus and induction therapy with basiliximab and new guidelines for drug monitoring were implemented. Since then, routine surveillance bronchoscopies with BAL and biopsies on five occasions within the first year after transplant have been performed in all recipients of lung and heart–lung transplants at the Great Ormond Street Hospital for Children, London, UK. The aim of this study was to report the prevalence of ACR and bacterial, viral or fungal pathogens detected in asymptomatic children after lung transplantation and to compare this with the prevalence in children with symptoms since the implementation of our new treatment protocols in 2002.

Some of these results have previously been reported in abstract form at the International Society for Heart and Lung Transplantation 2006 Annual Meeting, Madrid, Spain.

METHODS

The study population comprised all paediatric patients undergoing single lung transplantation (SLTx) or double lung transplantation (DLTx) or heart–lung transplantation at the Great Ormond Street Hospital for Children over a 4-year period from January 2002 to December 2005. Data collected included

Abbreviations: ACR, acute cellular rejection; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; DLTx, double lung transplantation; ISHLT, International Society of Heart and Lung Transplantation; PCR, polymerase chain reaction; SLTx, single lung transplantation

demographics (sex, age), patients' underlying diagnosis and type of transplant. All transplants were matched for blood group, but not for human leucocyte antigen.

This study was approved by the Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health Research Ethics Committee.

Transplant surgery was performed in standard fashion.[8] All patients received basiliximab as induction therapy, then triple immunosuppression with tacrolimus, azathioprine and prednisolone according to our standard protocol (available on request). We aim for tacrolimus trough concentrations of 12–15 ng/ml in the first 3 months after transplant, followed by target concentrations of 10–12 ng/ml for up to 1 year after transplant, and 8–10 ng/ml thereafter. Prednisolone is tapered down to 0.5 mg/kg/day in the first 6 weeks after transplant, then down to 0.25 mg/kg/day for 6 months, and maintained on 0.1–0.15 mg/kg/day indefinitely. A minimum of two anti-pseudomonal antibiotics was used in transplant recipients with cystic fibrosis, based on the recipient's most recent sputum culture results before transplant. Intravenous liposomal amphotericin was used in all transplant recipients with cystic fibrosis for the first week after transplant. Patients with cystic fibrosis and isolation of atypical mycobacteria before transplant were started on appropriate anti-mycobacterial therapy peri-operatively. In addition, all transplant recipients received teicoplanin on induction of anaesthesia and soon after transplant. All patients were started on anti-infective prophylactic treatment with co-trimoxazole and aciclovir, which were continued indefinitely, and nystatin for the first 3 months after transplant. In addition, oral itraconazole and nebulised colistin or amikacin were used for 3–6 months after transplant in recipients with cystic fibrosis. All our patients at high risk for CMV infection (defined as positive recipient or donor serology) received prophylaxis with oral ganciclovir (or valganciclovir since 2003) for a minimum of 3 months after transplant. All children underwent routine CMV monitoring in peripheral blood, performed weekly for the first 3 months, then monthly up to 1 year after transplant using qualitative polymerase chain reaction (PCR) in the early part of the study (until 2002) and quantitative real-time PCR thereafter (since 2003).

Surveillance bronchoscopies with BAL and biopsies were routinely performed in all transplant recipients during the first year after transplantation (1 week, and 1, 3, 6 and 12 months after transplant). Surveillance bronchoscopies with BAL and biopsies are not performed beyond 12 months after transplant in our institution. Bronchoscopies were classified according to whether subjects were asymptomatic or symptomatic at the time of the surveillance procedure, defined as the presence of cough, sputum production, dyspnoea, malaise, chest radiograph changes or >10% decline in forced expiratory volume in 1 s. Laboratory spirometry was performed according to our laboratory protocols, which are based on adult American Thoracic Society and European Respiratory Society standards for spirometry.[9–11] Spirometry was performed weekly in the first 3 months after transplant and at least monthly thereafter. In addition, any suspicious clinical changes after transplant prompted bronchoscopy with BAL and biopsies as well, but these clinically indicated procedures were not included in this study.

Two operators (PA and CB) performed all bronchoscopies. Nearly all bronchoscopies were carried out under general anaesthesia through a laryngeal mask. An adult-size fibreoptic bronchoscope with an outer diameter of 4.9 mm (Olympus BF Type P40, Olympus Medical Systems, Tokyo, Japan) was used and biopsies were performed with an alligator jaw-step biopsy forceps (Olympus FB-211D). In only eight bronchoscopies of children with <25 kg of body weight, we had to use a paediatric bronchoscope with an outer diameter of 3.6 mm (Olympus BF Type 3C40) and a small biopsy forceps (Olympus FB-15C) through the 1.2-mm instrument channel.

Biopsies were performed under fluoroscopic guidance from the lung periphery of either the right or the left lower lobe. We aimed to obtain at least five specimens of tissue for histopathological evaluation. The tissue specimens were fixed in 10% formaldehyde solution, and then serially sectioned and routinely stained with haematoxylin and eosin, elastic van Gieson, periodic acid-Schiff, reticulin and Grocott. The histopathological diagnosis of ACR was based on the working formulation for the classification of pulmonary allograft rejection from the Lung Rejection Study Group of the ISHLT: grade A0 = no significant abnormality; grade A1 = minimal; grade A2 = mild; grade A3 = moderate; and grade A4 = severe.[12] In addition, further aspects of pulmonary allograft rejection were also graded according to the above ISHLT criteria: grade B0 = active airway damage without scarring; grade B1 = lymphocytic bronchitis; and grade B2 = lymphocytic bronchiolitis.[12]

BAL was performed by wedging the tip of the bronchoscope in the right upper lobe, right middle lobe or in the lingula. A volume of 10–20 ml of sterile 0.9% sodium chloride was instilled as one aliquot and retrieved by manual suction. BAL fluid was collected in a sterile container and processed. BAL fluid was examined microscopically as a direct wet preparation and after gram and Ziehl–Nielsen staining. BAL fluid was cultured semiquantitatively for bacteria and fungi including specific culture for mycobacteria and *Legionella pneumophilia*. The isolation of coagulase negative staphylococci on BAL culture was considered to be of doubtful clinical significance unless the pathogen was simultaneously cultured on peripheral blood culture. Isolation of viridans streptococci (normal mouth flora) was not regarded as of clinical relevance. *Candida albicans* and *Candida* species (non-albicans) were considered clinically relevant if there was additional evidence of invasive fungal infection (positive histopathology or blood culture). Blood cultures were taken only from children with clinical signs of sepsis, defined as pyrexia (peripheral body temperature >37.5°C), raised blood inflammatory markers or malaise.

The immunofluorescence technique was used for detecting adenovirus, influenza virus type A and B, parainfluenza virus type 1, 2 and 3, respiratory syncytial virus and *Pneumocystis carinii* in the BAL fluid. The early antigen fluorescent foci (DEAFF) test was used for detecting CMV in this study. Supplementary testing for viral DNA (CMV, Epstein–Barr virus, adenovirus) by PCR was performed if indicated, using qualitative PCR in the early part of the study (until 2002) and quantitative real-time PCR thereafter (since 2003).

All procedural complications were recorded.

Statistical analysis

The diagnostic yield of bronchoscopies in the two groups of subjects was compared using the χ^2 test, incorporating Yates' correction for continuity. Significance was accepted for $p<0.05$.

RESULTS

Study population

A total of 23 lung-transplant operations were performed between January 2002 and December 2005, of which 12 (52%) were DLTx, 10 (43%) heart–lung transplants and 1 (4%) SLTx. The SLTx was a boy with cystic fibrosis who had previous pneumonectomy. The median (range) age at transplant was 14.0 (4.9–17.3) years; there were 15 (65%) female and 8 (35%) male patients.

In all, 17 (74%) patients had cystic fibrosis, of which 14 were ΔF508-homozygotic. Five (22%) patients had primary or

secondary pulmonary hypertension and 1 (4%) had end-stage lung disease secondary to post-adenovirus lung damage and chronic aspiration pneumonia in infancy. Six patients with cystic fibrosis had chronic lung infection with *Pseudomonas aeruginosa* only three had chronically grown *P aeruginosa* and *Staphylococcus aureus*, one had *S aureus* only, one had methicillin-resistant *S aureus* and one had chronic lung infection with *P aeruginosa* and *Stenotrophomonas maltophilia*. Specimens from three transplant recipients with cystic fibrosis were found to have atypical mycobacteria before transplant on sputum culture, of which one had isolated *Mycobacterium avium intracellulare* and two had isolated *Mycobacterium abscessus*. One transplant recipient with cystic fibrosis had chronic lung infection with *Burkholderia multivorans* before transplant.

No patient died within the first year after transplant. However, one male patient with cystic fibrosis died at the age of 17.2 years due to fungal sepsis, 23 months after left SLTx and one female patient aged 16.7 years died 27 months after DLTx for cystic fibrosis due to chronic graft failure.

Transbronchial biopsy and BAL results

A total of 95 bronchoscopies with biopsies and BAL were performed as routinely scheduled surveillance procedures, of which 69 (73%) were performed in subjects classified as asymptomatic and 26 (27%) in those with symptoms. A median of five biopsies were performed per patient (range 2–5).

ACR ⩾ A2 was diagnosed in 3 of 69 (4%) biopsies of asymptomatic subjects, and in 3 of 26 (12%) biopsies of subjects with symptoms (table 1). These episodes of ACR were treated with a minimum 3-day course of high-dose intravenous methylprednisolone (10 mg/kg/day). In addition, ACR = A1 was diagnosed in 5 of 69 (7%) biopsies of asymptomatic children, and in 4 of 26 (15%) of biopsies of children with symptoms. In response to these results, maintenance immunosuppression was tapered down more slowly. In one case, a grade A1 rejection in an asymptomatic patient 1 week after transplant progressed to a grade A2 rejection on surveillance biopsy follow-up 1 month after transplant. At that time, the child presented with respiratory symptoms and decreased lung function.

In nine patients, biopsy samples showed lymphocytic bronchitis/bronchiolitis (grade⩾B1). However, immunosuppression was not augmented in these patients.

Due to small biopsy sample size, no grading (ISHLT Lung Rejection Study Group classification of pulmonary allograft rejection) was given for 11 patients. However, there was no histological evidence of ACR in any of these patients. Seven of the subjects were classified as asymptomatic and four as having symptoms. If these 11 patients were excluded from the analysis, ACR⩾A2 was diagnosed in 3 of 62 (5%) biopsies in asymptomatic subjects and in 3 of 22 (14%) of biopsies subjects with symptoms. In only one of these cases was a paediatric bronchoscope used.

Table 1 Results of transbronchial biopsy and bronchoalveolar lavage in asymptomatic subjects (group 1) and subjects with symptoms (group 2)

	Group 1 (%)	Group 2 (%)
Acute rejection (⩾A2)	3 (4)	3 (12)
Acute rejection (=A1)	5 (7)	4 (15)
Isolation of pathogen	20 (29)	18 (69)
ACR/isolation of pathogen	24 (35)	22 (85)*
Total	69	26

ACR, acute cellular rejection.
*p<0.001.

Bacterial, viral or fungal pathogens were detected in 20 of 69 (29%) asymptomatic children and in 18 of 26 (69%) children with symptoms (table 1). More than one pathogen was detected in 11 patients.

Bacteria were the most frequently isolated pathogens in BAL fluid. Bacterial pathogens were detected in 16 of 69 (23%) asymptomatic children, and in 17 of 26 (65%) children with symptoms. Table 2 lists the different bacterial pathogens. Of the bacterial pathogens, >95% were detected in lung transplant recipients with cystic fibrosis; no bacteria were detected in blood cultures taken simultaneously. All children with isolation of bacterial pathogens in BAL fluid were treated with either an appropriate oral or intravenous antibiotic course even if infection was subclinical.

Viral pathogens were detected in 4 of 69 (6%) asymptomatic children, and in 4 of 26 (15%) children with symptoms. Table 2 lists the viral pathogens. All children detected with CMV in BAL fluid were donor–recipient CMV mismatches; two children had a breakthrough CMV infection despite oral prophylactic ganciclovir or valganciclovir. All patients detected with CMV received a 2–3-week course of intravenous ganciclovir followed by oral ganciclovir or valganciclovir for a further 3 months. CMV monitoring in peripheral blood was performed up to twice weekly in these patients until CMV DNA was undetectable.

Fungi were detected in four patients: two asymptomatic children and two children with symptoms. Table 2 lists the fungal species. None of the fungal pathogens were related to invasive fungal infection.

P carinii was detected in only one case of an asymptomatic child 6 months after transplant; this female patient with pulmonary hypertension received a sequential bilateral lung transplant at the age of 4.9 years. In this case, co-trimoxazole prophylaxis had been withheld for 2 months due to drug-induced neutropenia. The patient was treated with high-dose co-trimoxazole (120 mg/kg/day) for 3 weeks after detection of *P carinii* in the BAL fluid. Airway complications that needed interventional therapy were detected in two patients (one anastomotic airway stenosis and one bronchomalacia of the left main bronchus). Balloon dilatation was successfully performed to overcome the anastomotic stenosis; a stent insertion was required to improve the airway obstruction due to bronchomalacia.

Table 2 Bacterial, viral and fungal pathogens detected in the bronchoalveolar lavage specimens of all 95 bronchoscopies performed in the study

Pseudomonas aeruginosa	18
*Staphylococcus aureus**	11
Citrobacter freundii	3
Stenotrophomonas maltophilia	3
Pandoraea species	2
Achromobacter xylosoxidans	1
Ralstonia pickettii	1
Burkholderia multivorans	1
Moraxella catarrhalis	1
Morganella morganii	1
Pneumocystis carinii	1
Staphylococcus epidermidis	5
Viridans streptococci	7
Other	3
Cytomegalovirus	4
Parainfluenza virus-2	1
Influenza virus A	1
Influenza virus B	1
Candida albicans/non-albicans	3
Aspergillus fumigatus	1

*Including two methicillin-resistant *Staphylococcus aureus*.

The overall diagnostic yield was 35% (24/69) for asymptomatic children and 85% (22/26) for children with symptoms ($p<0.001$).

No lethal complications occurred due to surveillance bronchoscopies. One patient had moderate bleeding after biopsy (estimated blood loss 100–200 ml), but no blood transfusion was indicated. A pneumothorax requiring chest tube insertion occurred in one case. One patient had a minor aspiration after anaesthesia in the recovery room while sitting upright. A chest radiograph showed radiological features compatible with right lower lobe aspiration pneumonia in this case, but no treatment was required. The overall complications rate was 3.2%.

DISCUSSION

To our knowledge, this is the first study comparing the prevalence of ACR and subclinical graft infection in asymptomatic and symtomatic paediatric lung transplant recipients in the era of modern immunosuppression in a single centre applying a uniform management approach. This retrospective analysis has shown that many children have silent rejection or subclinical infection in the first year after lung transplantation.

Transplantation has been used as a therapy for end-stage lung disease since the early 1980s, and has by now become an accepted therapeutic option, even in the paediatric age group. Despite improved short-term survival due to improved surgical techniques, organ preservation and intensive care, long-term outcome after lung or heart–lung transplantation remains poor. The major obstacles to improved long-term survival are ACR and infection, and the subsequent development of bronchiolitis obliterans.[2 3] The underlying mechanism of this graft deterioration is unknown, but many risk factors are reported.[5] The single, most important factor for the development of bronchiolitis obliterans is the frequency and severity of ACR. However, non-alloimmunological factors such as bacterial, viral and fungal infections may also have a role.[4] It remains uncertain whether ACR in children is more frequent compared with adults. It is important to recognise that differentiation between ACR and infection in children and adults is nearly impossible, as clinical signs and symptoms are non-specific in both groups. However, it is unknown whether children report symptoms less frequently compared with adults. As there is a lack of a valuable surrogate marker to reliably distinguish ACR from infection, bronchoscopy with biopsy and BAL has remained the gold standard.[4 13 14]

By means of routine surveillance bronchoscopies, we aim to reduce the incidence of bronchiolitis obliterans due to earlier detection of ACR and subsequent augmentation of immunosuppression. However, the role of surveillance bronchoscopies with biopsy and BAL in asymptomatic lung transplant recipients has remained a controversial issue up to now. Valentine *et al*[15] estimated that >50% of adult lung transplant centres in the ISHLT perform regularly scheduled bronchoscopies. According to a recent informal survey of paediatric lung transplant centres participating in the International Paediatric Lung Transplant Collaborative, three quarters of the centres perform routine surveillance bronchoscopies for at least the first year after transplant. Three centres continue surveillance bronchoscopies for an extended period >1 year (A Faro, personal communication, 2005).

To our knowledge, there are 11 published studies (four prospective, seven retrospective) regarding the role of transbronchial biopsies in lung transplant recipients. The studies have different study designs, end points and durations of follow-up.[16–20] Taking these studies together, surveillance biopsies detected ACR (≥grade A2) in approximately 13.6% of clinically silent cases, the majority within the first 4–6 months after transplant.[21] Previous studies by Valentine *et al* and Tamm *et al* reported the success of lung transplantation in adult recipients without surveillance biopsies, although these studies have limitations. Valentine *et al*[15] used pooled data from the ISHLT Registry as their control group and therefore it is not a homogeneous cohort. Tamm *et al*[18] used historical controls instead.

There is only one published study investigating the role of surveillance bronchoscopies in detecting ACR in children after lung transplantation. Visner *et al* from the University of Florida reported the incidence of ACR (≥ grade A2) in 393 biopsies performed in paediatric lung transplant recipients. Only 25% of biopsies were performed for surveillance, but 38% as ACR treatment follow-up and 37% in patients with symptoms. ACR was found in 24% of surveillance procedures. Results of BAL to rule out infection were not reported. The incidence of complications in this study was 1.8%.[7]

We found an incidence of ACR (≥ grade A2) of 12% in children with symptoms compared with 4% in asymptomatic children. In addition, the incidence of ACR (grade A1) was 15% in patients with symptoms and 7% in asymptomatic patients. The importance of grade A1 ACR remains controversial, although a previous prospective study from Toronto reported that 22% of grade A1 rejection episodes progressed to a higher-grade ACR within 3 months.[22] We found progression of grade A1 ACR to a higher-grade ACR in only one case.

In our study, we detected lymphocytic bronchitis/bronchiolitis (≥ grade B1) in nine biopsies, just more than half in asymptomatic children. The relevance of lymphocytic bronchitis/bronchiolitis is unknown. Previously, Yousem[23] reported the likelihood of ACR following the development of lymphocytic bronchitis, which responds to augmented immunosuppression, but further details are not known.

We report evidence of infection (bacterial, viral or fungal) in more than two thirds of children with symptoms, and also isolation of pathogens in nearly one third of asymptomatic children. Without the use of routine surveillance bronchoscopies with BAL, subclinical infection would have remained undetected in many cases.

Apart from CMV, infection accounts for 37% of deaths during the first year after transplant, and for 19% between 3 and 5 years post transplant.[2] The risk of infection is much higher after lung transplantation compared with any other type of solid organ transplantation. In addition, the potential role of pathogens in the pathogenesis of bronchiolitis obliterans remains unclear. Bacterial and fungal infections are not known directly to contribute to the pathogenesis of bronchiolitis obliterans, although it may increase the risk of ACR.[24] *P aeruginosa* is often isolated from lung transplant recipients. It has been suggested that infections caused by pathogens such as *P aeruginosa* may be linked to bronchiolitis obliterans, but this remains uncertain. In contrast, CMV pneumonitis was correlated with the development of bronchiolitis obliterans in previous studies.[25]

Our study has some limitations. The sample size of our study population is small, and there is a lack of long-term follow-up. Despite this, our study offers the unique opportunity to show the positive effect of modern immunosuppression and a uniform management approach including routine surveillance bronchoscopy on short-term results in children after lung transplantation. The effect of routine surveillance bronchoscopy on long-term graft survival remains unproved though. Only 13 bronchoscopies with BAL and biopsies were performed in children at 12 months after transplant. Most subjects were asymptomatic (10/13). Nevertheless, five asymptomatic children had silent rejection or subclinical infection. The small number of subjects precludes statistical analysis, but these data suggest that surveillance bronchoscopy at 12 months after

transplant is justified. It could also be argued that the role of surveillance bronchoscopy in monitoring children>12 months after transplant should be re-examined.

In this study, the DEAFF test was routinely used for detecting CMV in BAL fluid, and for supplementary testing of quantitative viral load by real-time PCR in plasma, if indicated. However, Westall *et al*[26] recently showed that quantitative PCR analysis of CMV load in BAL fluid and the application of a diagnostic threshold are better predictors for the presence of histologically proved CMV infection, compared with detection of viral load in plasma. In our institution, quantitative measurements of CMV load by real-time PCR in BAL fluid are now routinely performed.

In conclusion, our data suggest that many children have silent rejection or subclinical infection in the first year after lung transplantation. Routine surveillance bronchoscopy allows detection and targeted therapy of these complications, and may therefore improve the long-term outcome after transplant.

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Appendix

Lung Cancer Screening Survey

Hello, my name is _____. I am calling for the Medical University of South Carolina and we are gathering information about health attitudes of residents of the United States.

Is this _____?

> **If No**, thank you very much but I must have misdialed. It is possible that your number may be called at another time. Good-bye.
>
> **If Yes**, continue ….

How many people live in your household that are 40 years of age or more?
_____

> **If 0**, Thank you, but we are only interviewing persons 40 years old and older. Good-bye.
>
> **If greater than 40**, continue …..

May I speak to the person of those 40 and older who most recently had a birthday?

If already speaking to selected person, continue with: You have been randomly selected to be interviewed and I'd like to ask some questions about your health and health practices. This interview will take less than 5 minutes and all answers will be kept confidential. You don't have to answer any questions you don't want to and you can end this interview at any time. If you have any questions about this survey I will be happy to give you a telephone number you can call to get more information [Dr Zoller @ 1-843-766-5777] Is now a good time to talk?

If correct person must be summoned, continue with: Hello, my name is _____. I am calling for the Medical University of South Carolina and we are gathering information about health attitudes of residents of the United States. You have been randomly selected to be interviewed and I'd like to ask some questions about your health and health practices. This interview will take less than 5 minutes and all answers will be kept confidential. You don't have to answer any questions you don't want to and you can end this interview at any time. If you have any questions about this survey I will be happy to give you a telephone number you can call to get more information [Dr Zoller @ 1-843-766-5777] Is now a good time to talk?

If person says now is not a good time to talk, ask when you call back.

1. How old were you on your last birthday? _____

2. Gender [do not ask]
   a) Male
   b) Female

3. In general, compared to other people your age, would you say that your health is
   a) Excellent
   b) Very good
   c) Good
   d) Fair
   e) Poor

4. Has a doctor ever told you that you had any cancer?
   a) Yes → What kind of cancer?
   _____
   b) No

5. Have you smoked over 100 ci
   a) Yes
   b) No [skip to Question 9]

6. Do you currently smoke cigarettes?
   a) Yes
   b) No [skip to Question 9]

7. On average, how many cigarettes do you now smoke per day?

   _____ cigarettes

8. For about how many years have you smoked this amount?

   _____ years

9. Is there a particular clinic, health center, doctor's office or other place that you usually go to if you are sick or need advice about your health?
   a) Yes
   b) No

10. What kind of place is it?
    a) Doctor's office, group practice or HMO
    b) A rural health clinic or health department
    c) Hospital Emergency Room
    d) A clinic in a hospital
    e) Other

11. Approximately how far away (in miles) do you live from this place?

    _____ miles

12. How long (in minutes), on average, does it take you to get to this place?

    _____ minutes

13. Does any health impairment keep you from working at a job or business?
    a) Yes
    b) No

14. Does any health impairment limit in any way the kind or amount of work you could do?
    a) Yes
    b) No

15. Has a doctor or other health professional ever told you that you are at high risk for lung cancer?
    a) Yes
    b) No

16. Do you think that you are at risk for lung cancer?
    a) Yes
    b) No

17. If cancer of the lung is detected early, what is the person's chance of surviving?
    a) Good
    b) Fair
    c) Poor
    d) Don't know

A special new type of x-ray/CAT scan has been developed which can find small cancers in the lung. If this scan finds cancer when it is small doctors believe that chances of curing the cancer is much better.

18. If you were told that you were at risk for lung cancer, would you consider having this scan done to determine the presence of lung cancer?
    a) Yes
    b) No

19. How important is cost to you in making a decision to have this scan?
    a) Very important
    b) Important
    c) Neutral

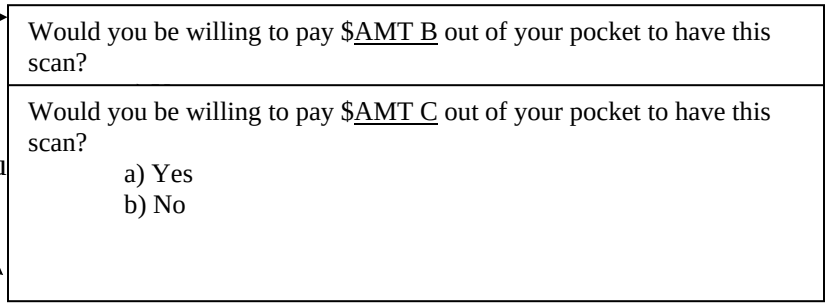
d) Not important
e) Very unimportant

20. How important is convenience to you in making a decision to have this scan?
    a) Very important
    b) Important
    c) Neutral
    d) Not important
    e) Very unimportant

21. How important is the risk of disease to you in making a decision to have this scan?
    a) Very important
    b) Important
    c) Neutral
    d) Not important
    e) Very unimportant

22. How important is the accuracy of the test to you in making a decision to have this scan?
    a) Very important
    b) Important
    c) Neutral
    d) Not important
    e) Very unimportant

23. Would you be willing to pay $<u>AMT A</u> out of your pocket to have this scan?
    a) Yes
    b) No



24. If a doctor told you that you
    treatment?
    a) Yes
    b) No

25. What is your race? Would you say ….
    a) American Indian or Alaskan Native
    b) Asian or Pacific Islander
    c) Black or African-American
    d) White
    e) Another race

26. What is your marital status?
    a) Married
    b) Single
    c) Divorced

d) Widowed
e) Separated

27. What is the highest level of education you have completed?
    a) Did not complete high school
    b) Completed high school
    c) Some college or technical school
    d) Completed college

28. What type of health coverage do you use to pay for most of your medical care? Is it coverage through ….
    a) Your employer
    b) Someone else's employer
    c) A plan that you or someone else buys on your own
    d) Medicare
    e) Medicaid or Medical Assistance
    f) The military, CHAMPUS or the VA
    g) The Indian Health Service
    h) Some other source
    i) None
    j) Don't know/Not sure
    k) Refused

29. Is that an HMO type insurance plan, or a traditional (fee-for-service) insurance plan?
    a) HMO
    b) Traditional
    c) Don't know
    d) Refused

30. What is your work status?
    a) Employed full-time
    b) Employed part-time
    c) Home maker
    d) In school
    e) Retired from formal employment
    f) Not working, but looking for a job
    g) Not working, but not looking for a job
    h) Don't know

31. Are you the person in your household who owns or rents your home"
    a) Yes
    b) No
    c) Don't know
    d) Refused

32. What is your total annual household income?
    a) $0 - $19,999
    b) $20,000 to $29,999
    c) $30,000 to $39,999
    d) $40,000 to $59,999
    e) $60,000 to $79,999
    f) $80,000 to $99,999
    g) $100,000 or greater
    h) Refused

33. Are you the primary income source for your household?
    a) Yes
    b) No
    c) Don’t know
    d) Refused

That was my last question. Thank you for your participation is our survey. Your answers will be kept confidential and combined with the answers of others to determine more about the health practices of the United States residents. Good-bye.